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NEWS 26 Oct 01 CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27 Oct 21 EVENTLINE has been reloaded
NEWS 28 Oct 24 BEILSTEIN adds new search fields
NEWS 29 Oct 24 Nutraceuticals International (NUTRACEUT) now available on STN
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NEWS 32 Nov 25 More calculated properties added to REGISTRY
NEWS 33 Dec 02 TIBKAT will be removed from STN
NEWS 34 Dec 04 CSA files on STN
NEWS 35 Dec 17 PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36 Dec 17 TOXCENTER enhanced with additional content
NEWS 37 Dec 17 Adis Clinical Trials Insight now available on STN
NEWS 38 Dec 30 ISMEC no longer available
NEWS 39 Jan 21 NUTRACEUT offering one free connect hour in February 2003
NEWS 40 Jan 21 PHARMAML offering one free connect hour in February 2003
NEWS 41 Jan 29 Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 42 Feb 13 CANCERLIT is no longer being updated
NEWS 43 Feb 24 METADEX enhancements
NEWS 44 Feb 24 PCTGEN now available on STN
NEWS 45 Feb 24 TEMA now available on STN
NEWS 46 Feb 26 NTIS now allows simultaneous left and right truncation
NEWS 47 Feb 26 PCTFULL now contains images
NEWS 48 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 49 Mar 19 APOLLIT offering free connect time in April 2003
NEWS 50 Mar 20 EVENTLINE will be removed from STN
NEWS 51 Mar 24 PATDPAFULL now available on STN
NEWS 52 Mar 24 Additional information for trade-named substances without structures available in REGISTRY
NEWS 53 Mar 24 Indexing from 1957 to 1966 added to records in CA/CAPLUS

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L1 381 PERK OR TYPE I TRANSMEMBRANE SERINE THREONINE KINASE

=> s l1 and (knockout or knock out or transgen? or disrupt? or deficien? or deleti?)
L2 46 L1 AND (KNOCKOUT OR KNOCK OUT OR TRANSGEN? OR DISRUPT? OR DEFICI
EN? OR DELETI?)

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L3 24 DUP REM L2 (22 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2003:128287 BIOSIS
DN PREV200300128287
TI Functional characterization of Drosophila melanogaster ***PERK*** eukaryotic initiation factor 2alpha (eIF2alpha) kinase.
AU Pomar, Natalia; Berlanga, Juan J.; Campuzano, Sonsoles; Hernandez, Greco; Elias, Monica; de Haro, Cesar (1)
CS (1) Centro de Biologia Molecular 'Severo Ochoa', Facultad de Ciencias, CSIC-UAM, Cantoblanco, Madrid, 28049, Spain: cdeharo@cbm.uam.es Spain
SO European Journal of Biochemistry, (January 2003, 2003) Vol. 270, No. 2, pp. 293-306. print.
ISSN: 0014-2956.
DT Article
LA English
AB Four distinct eukaryotic initiation factor 2alpha (eIF2alpha) kinases phosphorylate eIF2alpha at S51 and regulate protein synthesis in response to various environmental stresses. These are the hemin-regulated inhibitor (HRI), the interferon-inducible dsRNA-dependent kinase (PKR), the endoplasmic reticulum (ER)-resident kinase (***PERK***) and the GCN2 protein kinase. Whereas HRI and PKR appear to be restricted to mammalian cells, GCN2 and ***PERK*** seem to be widely distributed in eukaryotes. In this study, we have characterized the second eIF2alpha kinase found in Drosophila, a ***PERK*** homologue (DPERK). Expression of DPERK is developmentally regulated. During embryogenesis, DPERK expression becomes concentrated in the endodermal cells of the gut and in the germ line precursor cells. Recombinant wild-type DPERK, but not the inactive DPERK-K671R mutant, exhibited an autokinase activity, specifically phosphorylated Drosophila eIF2alpha at S50, and functionally replaced the endogenous Saccharomyces cerevisiae GCN2. The full length protein, when expressed in 293T cells, located in the ER-enriched fraction, and its subcellular localization changed with ***deletion*** of different N-terminal fragments. Kinase activity assays with these DPERK ***deletion*** mutants suggested that DPERK localization facilitates its in vivo function. Similar to mammalian ***PERK*** , DPERK forms oligomers in vivo and DPERK activity appears to be regulated by ER stress. Furthermore, the stable complexes between wild-type DPERK and DPERK-K671R mutant were mediated through the N terminus of the proteins and exhibited an in vitro eIF2alpha kinase activity.

L3 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:906548 CAPLUS
DN 138:290
TI Methods of screening test substances for treating or preventing diseases involving an oxidative stress
IN Ron, David; Harding, Heather P.
PA New York University, USA
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE
---------- ---- -------- ---------- --------

PI WO 2002095061 A1 20021128 WO 2002-US15766 20020517
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003008272 A1 20030109 US 2002-150759 20020517
PRAI US 2001-292054P P 20010518
AB The invention is directed to methods for identifying test substances useful for the prevention or treatment of diseases involving an oxidative stress. The methods involve screening assays, including high throughput screening techniques, in which the test substances are tested for their ability to promote resistance to oxidative stress by activating one or more points of the integrated stress response pathway, while not causing stress.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:51200 CAPLUS
DN 136:117362
TI Alphavirus vectors and virosomes with modified HIV genes for use as vaccines
IN Olmsted, Robert; Keith, Paula; Dryga, Sergey; Caley, Ian; Maughan, Maureen; Johnston, Robert; Davis, Nancy; Swanstrom, Ronald
PA Alphavax, Inc., USA; University of North Carolina at Chapel Hill
SO PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3
PATENT NO. KIND DATE APPLICATION NO. DATE
PI WO 2002003917 A2 20020117 WO 2001-US21701 20010709
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 2001073313 A5 20020121 AU 2001-73313 20010709
PRAI US 2000-216995P P 20000707
WO 2001-US21701 W 20010709
AB The present invention provides methods and compns. comprising a population of alphavirus replicon particles comprising two or more isolated nucleic acids selected from (1) an isolated nucleic acid encoding an env gene product or an immunogenic fragment thereof of a human immunodeficiency virus, (2) an isolated nucleic acid encoding a gag gene product or an immunogenic fragment thereof of a human immunodeficiency virus, wherein the gag gene product or immunogenic fragment thereof is modified to inhibit formation of virus-like particles contg. the gag gene product or the immunogenic fragment thereof and their release from a cell, and (3) an isolated nucleic acid encoding a pol gene product or an immunogenic fragment thereof of a human immunodeficiency virus, wherein the pol gene product or immunogenic fragment thereof is modified to inhibit integrase, Rnase H and/or reverse transcriptase activity, and wherein the nucleic acids are each contained within a sep. alphavirus replicon particle.

L3 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:638353 CAPLUS
DN 137:180792
TI ***Transgenic*** mice containing type I transmembrane ER-resident serine/threonine protein kinase gene ***PERK*** ***disruptions*** and their use as disease models and for screening for modulators
IN Allen, Keith D.; Wiles, Michael V.
PA USA
SO U.S. Pat. Appl. Publ., 34 pp., which which which
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE
PI US 2002116730 A1 20020822 US 2001-5983 20011107
PRAI US 2000-246676P P 20001107
US 2001-311018P P 20010808
US 2001-324765P P 20010924
US 2001-326148P P 20010928
AB The present invention relates to ***transgenic*** animals, as well as compns. and methods relating to the characterization of gene function. Specifically, the present invention provides ***transgenic*** mice comprising a ***disruption*** in the ***PERK*** gene encoding a type I transmembrane endoplasmic reticulum-resident serine-threonine protein kinase, which is known to phosphorylate protein formation initiation factor eIF2-.alpha.. To investigate the role of ***PERK*** , ***disruptions*** in the ***PERK*** genes are produced by homologous recombination using 5' and 3' arms in a targeting construct. The ***transgenic*** mice exhibit seizure-like responses at a lower doses of Metrazol, relative to a wild-type mouse. Such ***transgenic*** mice are useful as models for disease and for identifying agents that modulate gene expression and gene function, and as potential treatments for various disease states and disease conditions.

L3 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:398652 BIOSIS
DN PREV200200398652
TI Dimerization and release of molecular chaperone inhibition facilitate activation of eukaryotic initiation factor-2 kinase in response to endoplasmic reticulum stress.
AU Ma, Kun; Vattem, Krishna M.; Wek, Ronald C. (1)
CS (1) Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, 46202: rwek@iupui.edu USA
SO Journal of Biological Chemistry, (May 24, 2002) Vol. 277, No. 21, pp. 18728-18735. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Phosphorylation of eukaryotic initiation factor-2 (eIF2) by pancreatic eIF2 kinase (PEK), induces a program of translational expression in response to accumulation of malfolded protein in the endoplasmic reticulum (ER). This study addresses the mechanisms activating PEK, also designated ***PERK*** or EIF2AK3. We describe the characterization of two regions in the ER luminal portion of the transmembrane PEK that carry out distinct functions in the regulation of this eIF2 kinase. The first region mediates oligomerization between PEK polypeptides, and ***deletion*** of this portion of PEK blocked induction of eIF2 kinase activity. The second characterized region of PEK facilitates interaction with ER chaperones. In the absence of stress, PEK associates with ER chaperones GRP78 (BiP) and GRP94, and this binding is released in response to ER stress. ER luminal sequences flanking the transmembrane domain are required for GRP78 interaction, and ***deletion*** of this portion of PEK led to its activation even in the absence of ER stress. These results suggest that this ER chaperone serves as a repressor of PEK activity, and release of ER chaperones from PEK when misfolded proteins accumulate in the ER induces gene expression required to enhance the protein folding capacity of the ER.

L3 ANSWER 6 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2003:71647 BIOSIS
DN PREV200300071647
TI Control of ***PERK*** eIF2alpha kinase activity by the endoplasmic reticulum stress-induced molecular chaperone P58IPK.
AU Yan, Wei (1); Frank, Christopher L.; Korth, Marcus J.; Sopher, Bryce L.; Novoa, Isabel; Ron, David; Katze, Michael G.
CS (1) Department of Microbiology, University of Washington, Box 358070, Seattle, WA, 98195-8070, USA: wyan96@u.washington.edu USA
SO Proceedings of the National Academy of Sciences of the United States of America, (December 10 2002) Vol. 99, No. 25, pp. 15920-15925. print.
ISSN: 0027-8424.
DT Article
LA English
AB P58IPK is an Hsp40 family member known to inhibit the interferon (IFN)-induced, double-stranded RNA-activated, eukaryotic initiation factor 2alpha (eIF2alpha) protein kinase R (PKR) by binding to its kinase domain. We find that the stress of unfolded proteins in the endoplasmic reticulum (ER) activates P58IPK gene transcription through an ER stress-response element in its promoter region. P58IPK interacts with and inhibits the PKR-like ER-localized eIF2alpha kinase ***PERK*** , which is normally activated during the ER-stress response to protect cells from ER stress by attenuating protein synthesis and reducing ER client protein load. Levels of phosphorylated eIF2alpha were lower in ER-stressed P58IPK-overexpressing cells and were enhanced in P58IPK mutant cells. In the ER-stress response, PKR-like ER kinase (***PERK***)-mediated translational repression is transient and is followed by translational recovery and enhanced expression of genes that increase the capacity of the ER to process client proteins. The absence of P58IPK resulted in increased expression levels of two ER stress-inducible genes, BiP and Chop, consistent with the enhanced eIF2alpha phosphorylation in the P58IPK ***deletion*** cells. Our studies suggest that P58IPK induction during the ER-stress response represses ***PERK*** activity and plays a functional role in the expression of downstream markers of ***PERK*** activity in the later phase of the ER-stress response.

L3 ANSWER 7 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2002:564977 BIOSIS
DN PREV200200564977
TI Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase ***PERK*** and phosphorylation of the translation initiation factor eIF2alpha.
AU Koumenis, Constantinos (1); Naczki, Christine; Koritzinsky, Marianne; Rastani, Sally; Diehl, Alan; Sonenberg, Nahum; Koromilas, Antonis;

Wouters, Bradly G.
CS (1) Departments of Radiation Oncology and Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC, 27157: ckoumeni@wfubmc.edu USA
SO Molecular and Cellular Biology, (November, 2002) Vol. 22, No. 21, pp. 7405-7416. http://mcb.asm.org/. print.
ISSN: 0270-7306.
DT Article
LA English
AB Hypoxia profoundly influences tumor development and response to therapy. While progress has been made in identifying individual gene products whose synthesis is altered under hypoxia, little is known about the mechanism by which hypoxia induces a global downregulation of protein synthesis. A critical step in the regulation of protein synthesis in response to stress is the phosphorylation of translation initiation factor eIF2alpha on Ser51, which leads to inhibition of new protein synthesis. Here we report that exposure of human diploid fibroblasts and transformed cells to hypoxia led to phosphorylation of eIF2alpha, a modification that was readily reversed upon reoxygenation. Expression of a transdominant, nonphosphorylatable mutant allele of eIF2alpha attenuated the repression of protein synthesis under hypoxia. The endoplasmic reticulum (ER)-resident eIF2alpha kinase ***PERK*** was hyperphosphorylated upon hypoxic stress, and overexpression of wild-type ***PERK*** increased the levels of hypoxia-induced phosphorylation of eIF2alpha. Cells stably expressing a dominant-negative ***PERK*** allele and mouse embryonic fibroblasts with a homozygous ***deletion*** of ***PERK*** exhibited attenuated phosphorylation of eIF2alpha and reduced inhibition of protein synthesis in response to hypoxia. ***PERK*** -/- mouse embryo fibroblasts failed to phosphorylate eIF2alpha and exhibited lower survival after prolonged exposure to hypoxia than did wild-type fibroblasts. These results indicate that adaptation of cells to hypoxic stress requires activation of ***PERK*** and phosphorylation of eIF2alpha and suggest that the mechanism of hypoxia-induced translational attenuation may be linked to ER stress and the unfolded-protein response.

L3 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2002:318997 BIOSIS
DN PREV200200318997
TI The ***PERK*** eukaryotic initiation factor 2alpha kinase is required for the development of the skeletal system, postnatal growth, and the function and viability of the pancreas.
AU Zhang, Peichuan; McGrath, Barbara; Li, Sheng'ai; Frank, Ami; Zambito, Frank; Reinert, Jamie; Gannon, Maureen; Ma, Kun; McNaughton, Kelly; Cavener, Douglas R. (1)
CS (1) Department of Biology, The Pennsylvania State University, 208 Mueller Lab, University Park, PA, 16802: drc9@psu.edu USA
SO Molecular and Cellular Biology, (June, 2002) Vol. 22, No. 11, pp. 3864-3874. http://mcb.asm.org/. print.
ISSN: 0270-7306.
DT Article
LA English
AB Phosphorylation of eukaryotic initiation factor 2alpha (eIF-2alpha) is typically associated with stress responses and causes a reduction in protein synthesis. However, we found high phosphorylated eIF-2alpha (eIF-2alpha(P)) levels in nonstressed pancreata of mice. Administration of glucose stimulated a rapid dephosphorylation of eIF-2alpha. Among the four eIF-2alpha kinases present in mammals, ***PERK*** is most highly expressed in the pancreas, suggesting that it may be responsible for the high eIF-2alpha(P) levels found therein. We describe a ***Perk*** ***knockout*** mutation in mice. Pancreata of ***Perk*** -/- mice are morphologically and functionally normal at birth, but the islets of Langerhans progressively degenerate, resulting in loss of insulin-secreting beta cells and development of diabetes mellitus, followed later by loss of glucagon-secreting alpha cells. The exocrine pancreas exhibits a reduction in the synthesis of several major digestive enzymes and succumbs to massive apoptosis after the fourth postnatal week. ***Perk*** -/- mice also exhibit skeletal dysplasias at birth and postnatal growth retardation. Skeletal defects include ***deficient*** mineralization, osteoporosis, and abnormal compact bone development. The skeletal and pancreatic defects are associated with defects in the rough endoplasmic reticulum of the major secretory cells that comprise the skeletal system and pancreas. The skeletal, pancreatic, and growth defects are similar to those seen in human Wolcott-Rallison syndrome.

L3 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:521732 CAPLUS
DN 137:230749
TI Loss of kinase activity in a patient with Wolcott-Rallison syndrome caused by a novel mutation in the EIF2AK3 gene
AU Biason-Lauber, Anna; Lang-Muritano, Mariarosaria; Vaccaro, Tindara; Schoenle, Eugen J.
CS Division of Pediatric Endocrinology/Diabetology, University Children's Hospital, Zurich, 8032, Switz.
SO Diabetes (2002), 51(7), 2301-2305
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
AB Wolcott-Rallison syndrome (WRS) is an autosomal recessive disorder characterized by neonatal or early infancy type 1 diabetes, epiphyseal dysplasia, and growth retardation. Mutations in the EIF2AK3 gene, encoding the eukaryotic initiation factor 2.alpha.-kinase 3 (EIF2AK3), have been found in WRS patients. Here we describe a girl who came to our attention at 2 mo of age with severe hypertonic dehydration and diabetic ketoacidosis. A diagnosis of type 1 diabetes was made and insulin treatment initiated. Growth retardation and microcephaly were also present. Anti-islet cell autoantibodies were neg., and mitochondrial diabetes was excluded. Imaging revealed a hypoplastic pancreas and typical signs of spondylo-epiphyseal dysplasia. The diagnosis of WRS was therefore made at age 5 yr. Sequencing anal. of her EIF2AK3 gene revealed the presence of a homozygous T to C exchange in exon 13 leading to the missense serine 877 proline mutation. The mutated kinase, although it partly retains the ability of autophosphorylation, is unable to phosphorylate its natural substrate, eukaryotic initiation factor 2.alpha. (eIF2.alpha.). This is the first case in which the pathophysiol. role of EIF2AK3 ***deficiency*** in WRS is confirmed at the mol. level. Our data demonstrate that EIF2AK3 kinase activity is essential for pancreas islet function and bone development in humans, and we suggest EIF2AK3 as a possible target for therapeutic intervention in diabetes.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:369670 BIOSIS
DN PREV200200369670
TI The cellular response to accumulation of unfolded proteins in the endoplasmic reticulum.
AU Kaufman, Randal J. (1)
CS (1) Biological Chemistry, Med School, HHMI/Univ.Mich, 1150 W Medical Center Drive, Ann Arbor, MI, 48109-0560 USA
SO FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A891. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DT Conference
LA English
AB The unfolded protein response (UPR) is an adaptive program activated by the accumulation of unfolded proteins in the endoplasmic reticulum (ER). In higher eukaryotes, there exist three ER-localized proximal sensors of the UPR; IRE1, ATF6, and ***PERK*** . On signaling the UPR, IRE1 protein kinase activates its endoribonuclease function to initiate a splicing reaction on an mRNA encoding a basic leucine zipper transcription factor that is sufficient for UPR transcriptional induction. In addition, the UPR induces proteolytic cleavage of the ER transmembrane activating transcription factor ATF6 to yield a cytosolic fragment that migrates to the nucleus and is required to activate transcription of the ER stress response genes. Activation of the UPR also results in a transient translation inhibition mediated by ***PERK*** , a protein kinase that phosphorylates the alpha subunit of the eukaryotic translation initiation factor 2 (eIF2a) on residue Ser51. Therefore, activation of ***PERK*** limits the amount of protein that requires folding under conditions of ER stress. Interestingly, this translational control is also required for maximal transcriptional activation of the ER stress response genes. We have studied the role of these individual pathways by analysis of genetic ***deficiencies*** in murine and C. elegans species in vivo. The results support that all three pathways are not only required for survival upon ER stress, but are also essential for development.

L3 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:375215 CAPLUS
DN 137:181405
TI RNA-dependent protein kinases
AU Petryshyn, Raymond A.; Nekhai, Sergie; Perez-Albuerne, Evelio D.
CS National Cancer Institute, Bethesda, MD, USA
SO Endocrine Updates (2002), 16(RNA Binding Proteins), 175-191
CODEN: ECUDF4; ISSN: 1566-0729
PB Kluwer Academic Publishers
DT Journal; General Review
LA English
AB A review. RNA mols. conduct various functions in living organisms by interacting with other biol. mols. The recognition of RNA mols., usually by proteins, is often dependent on the shape into which the RNA folds, rather than on any specific nucleotide sequence. This review focuses on double-stranded RNA (dsRNA) dependent protein kinase (PKR), which phosphorylates the .alpha. subunit of eukaryotic initiation factor-2 (eIF-2.alpha.). PKR contains 2 amino acid sequence motifs called dsRNA-binding motifs (DRBM) that allow binding to dsRNA and subsequently convert the protein from a latent to an active serine/threonine protein kinase. PKR is the only known kinase that depends on dsRNA for activation, although 2 closely related eIF-2.alpha. kinases, pancreatic eIF-2.alpha. kinase (PEK) and PKR-like endoplasmic reticulum kinase (***PERK***), have been described. PKR presents a unique paradigm for studying RNA:protein interaction because its activity depends on binding to dsRNA but not DNA, single-stranded RNA, or RNA:DNA hybrids. Well-known for mediating the antiviral effects of interferons (IFNs), PKR is also implicated in regulating cell differentiation, signal transduction, and in eliciting apoptosis in response to various stress induction agents. Although the protein is ubiquitous in cells, PKR activity is suppressed during cell proliferation and in tumor cells, suggesting a role for the kinase in the regulation of cell proliferation. This review summarizes the viral and cellular proteins and dsRNAs that activate and inhibit PKR,

and the most recent findings in PKR ***knockout*** mice.
RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2001:152848 CAPLUS
DN 134:218920
TI Brassica wounding- and pathogen-inducible proline-rich extensin-like receptor kinase PERK1 gene and ***transgenic*** plants expressing it
IN Goring, Daphne; Silva, Nancy
PA Can.
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001014563	A1	20010301	WO 2000-CA966	20000818

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-149466P P 19990819
US 1999-159122P P 19991013
AB The invention includes ***PERK*** (proline-rich extensin-like receptor kinase) nucleic acid mols. and polypeptides. A receptor-like protein kinase designated PERK1 (proline-rich extension-like receptor kinase 1) was isolated from an 8-pistil cDNA library of Brassica napus. The deduced PERK1 protein is comprised of a cytoplasmic domain that contains all of the conserved amino acids prevalent among serine/threonine kinases, a transmembrane domain and an extracellular domain with sequence similarity to the extensin family of plant cell wall proteins. Northern blot anal. demonstrated that PERK1 mRNA accumulated rapidly in leaf and stem tissue of B.napus in response to wounding and treatment with salicylic acid. In contrast, no significant accumulation of PERK1 mRNA was detected following treatment with Me jasmonate. The rapidity of PERK1 mRNA accumulation in response to these treatments shows a role in plant defense signaling.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 2002:190693 BIOSIS
DN PREV200200190693
TI Disturbed activation of endoplasmic reticulum stress transducers by familial Alzheimer's disease-linked presenilin-1 mutations.
AU Katayama, Taiichi; Imaizumi, Kazunori (1); Honda, Akiko; Yoneda, Takunari; Kudo, Takashi; Takeda, Masatoshi; Mori, Kazutoshi; Rozmahel, Richard; Fraser, Paul; St. George-Hyslop, Peter; Tohyama, Masaya
CS (1) Division of Structural Cell Biology, Nara Institute of Science and Technology (NAIST), 8916-5 Takayama, Ikoma, Nara, 630-0101: imaizumi@bs.aist-nara.ac.jp Japan
SO Journal of Biological Chemistry, (November 16, 2001) Vol. 276, No. 46, pp. 43446-43454. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Recent studies have shown independently that presenilin-1 (PS1) null mutants and familial Alzheimer's disease (FAD)-linked mutants should both down-regulate signaling of the unfolded protein response (UPR). However, it is difficult to accept that both mutants possess the same effects on the UPR. Furthermore, contrary to these observations, neither loss of PS1 and PS2 function nor expression of FAD-linked PS1 mutants were reported to have a discernable impact on the UPR. Therefore, re-examination and detailed analyses are needed to clarify the relationship between PS1 function and UPR signaling. Here, we report that PS1/PS2 null and dominant negative PS1 mutants, which are mutated at aspartate residue 257 or 385, did not affect signaling of the UPR. In contrast, FAD-linked PS1 mutants were confirmed to disturb UPR signaling by inhibiting activation of both Ire1alpha and ATF6, both of which are endoplasmic reticulum (ER) stress transducers in the UPR. Furthermore, PS1 mutants also disturbed activation of ***PERK*** (PKR-like ER kinase), which plays a crucial role in inhibiting translation during ER stress. Taken together, these observations suggested that PS1 mutations could affect signaling pathways controlled by each of the respective ER-stress transducers, possibly through a gain-of-function.

L3 ANSWER 14 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 2001:235047 BIOSIS
DN PREV200100235047
TI IRF3 and IRF7 phosphorylation in virus-infected cells does not require double-stranded RNA-dependent protein kinase R or IkappaB kinase but is blocked by vaccinia virus E3L protein.
AU Smith, Eric J.; Marie, Isabelle; Prakash, Arun; Garcia-Sastre, Adolfo; Levy, David E. (1)
CS (1) Dept. of Pathology, New York University School of Medicine, 550 First Ave., New York, NY, 10016: levyd01@med.nyu.edu USA
SO Journal of Biological Chemistry, (March 23, 2001) Vol. 276, No. 12, pp. 8951-8957. print.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB Induction of interferon-alpha (IFNalpha) gene expression in virus-infected cells requires phosphorylation-induced activation of the transcription factors IRF3 and IRF7. However, the kinase(s) that targets these proteins has not been identified. Using a combined pharmacological and genetic approach, we found that none of the kinases tested was responsible for IRF phosphorylation in cells infected with Newcastle disease virus (NDV). Although the broad-spectrum kinase inhibitor staurosporine potently blocked IRF3 and -7 phosphorylation, inhibitors for protein kinase-C, protein kinase A, MEK, SAPK, IKK, and protein kinase R (PKR) were without effect. Both IkappaB kinase and PKR have been implicated in IFN induction, but cells genetically ***deficient*** in IkappaB kinase, PKR, or the PKR-related genes ***PERK*** , IRE1, or GCN2 retained the ability to phosphorylate IRF7 and induce IFNalpha. Interestingly, PKR mutant cells were defective for response to double-stranded (ds) RNA but not to virus infection, suggesting that dsRNA is not the only activating viral component. Consistent with this notion, protein synthesis was required for IRF7 phosphorylation in virus-infected cells, and the kinetics of phosphorylation and viral protein production were similar. Despite evidence for a lack of involvement of dsrna and PKR, vaccinia virus E3L protein, a dsRNA-binding protein capable of inhibiting PKR, was an effective IRF3 and -7 phosphorylation inhibitor. These results suggest that a novel cellular protein that is activated by viral products in addition to dsrna and is sensitive to E3L inhibition is responsible for IRF activation and reveal a novel mechanism for the anti-IFN effect of E3L distinct from its inhibition of PKR.

L3 ANSWER 15 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 2001:471247 BIOSIS
DN PREV200100471247
TI Taurine prevents the decrease in expression and secretion of extracellular superoxide dismutase induced by homocysteine: Amelioration of homocysteine-induced endoplasmic reticulum stress by taurine.
AU Nonaka, Hidemi; Tsujino, Takeshi (1); Watari, Yasuhiro; Emoto, Noriaki; Yokoyama, Mitsuhiro
CS (1) Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki, Chuo, Kobe, 650-0017: hidemin@med.kobe-u.ac.jp Japan
SO Circulation, (September 4, 2001) Vol. 104, No. 10, pp. 1165-1170. print.
ISSN: 0009-7322.
DT Article
LA English
SL English
AB Background: Hyperhomocysteinemia is an independent risk factor for atherosclerosis. Homocysteine has been shown to induce endoplasmic reticulum (ER) stress in vascular endothelial cells. ER stress is a condition in which glycoprotein trafficking is ***disrupted*** and unfolded proteins accumulate in the ER. ER molecular chaperons, such as GRP78, are induced and an ER resident kinase, ***PERK*** , is activated when cells are subjected to ER stress. Conversely, taurine is reported to have antiatherogenic effects by unknown mechanisms. To elucidate the mechanisms by which homocysteine induces atherosclerosis and taurine prevents it, we examined whether homocysteine and taurine affect the expression and secretion of extracellular superoxide dismutase (EC-SOD), a glycoprotein secreted from vascular smooth muscle cells (VSMCs) that protects the vascular wall from oxidative stress. Methods and Results: We assessed the expression of EC-SOD and GRP78 mRNA in cultured rat VSMCs by
Northern blot analysis. The EC-SOD protein secreted into the culture medium was examined by Western blot analysis. Homocysteine (5 mmol/L) and other ER stress inducers, including A23187, were found to decrease EC-SOD mRNA expression and protein secretion. Furthermore, they upregulated GRP78 MRNA expression and activated ***PERK*** . Taurine (0.5 to 10 mmol/L), conversely, prevented these actions induced by homocysteine. Conclusions: Homocysteine induces ER stress and reduces the secretion and expression of EC-SOD in VSMCs, leading to increased oxidative stress in the vascular wall. Taurine restores the secretion and expression of EC-SOD by ameliorating ER stress induced by homocysteine.

L3 ANSWER 16 OF 24 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002132258 EMBASE
TI Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2.alpha..
AU Novoa I.; Zeng H.; Harding H.P.; Ron D.
CS D. Ron, New York University Medical Center, 540 First Ave., New York, NY 10016, United States. ron@saturn.med.nyu.edu
SO Journal of Cell Biology, (25 May 2001) 153/5 (1011-1021).
Refs: 42
ISSN: 0021-9525 CODEN: JCLBA3
CY United States
DT Journal; Article

FS 029 Clinical Biochemistry
LA English
SL English
AB Phosphorylation of the .alpha. subunit of eukaryotic translation initiation factor 2 (eIF2.alpha.) on serine 51 integrates general translation repression with activation of stress-inducible genes such as ATF4, CHOP, and BiP in the unfolded protein response. We sought to identify new genes active in this phospho-eIF2.alpha.-dependent signaling pathway by screening a library of recombinant retroviruses for clones that inhibit the expression of a CHOP::GFP reporter. A retrovirus encoding the COOH terminus of growth arrest and DNA damage gene (GADD)34, also known as
MYD116 (Fornace, A.J., D.W. Neibert, M.C. Hollander, J.D. Luethy, M. Papathanasiou, J. Fragoli, and N.J. Holbrook. 1989. Mol. Cell. Biol. 9:4196-4203; Lord K.A., B. Hoffman-Lieberman, and D.A. Lieberman. 1990. Nucleic Acid Res. 18:2823), was isolated and found to attenuate CHOP (also known as GADD153) activation by both protein malfolding in the endoplasmic reticulum, and amino acid deprivation. Despite normal activity of the cognate stress-inducible eIF2.alpha. kinases ***PERK*** (also known as PEK) and GCN2, phospho-eIF2.alpha. levels were markedly diminished in GADD34-overexpressing cells. GADD34 formed a complex with the catalytic subunit of protein phosphatase 1 (PP1c) that specifically promoted the dephosphorylation of eIF2.alpha. in vitro. Mutations that interfered with the interaction with PP1c prevented the dephosphorylation of eIF2.alpha. and blocked attenuation of CHOP by GADD34. Expression of GADD34 is stress dependent, and was absent in ***PERK*** (-/-) and GCN2(-/-) cells. These findings implicate GADD34-mediated dephosphorylation of eIF2.alpha. in a negative feedback loop that inhibits stress-induced gene expression, and that might promote recovery from translational inhibition in the unfolded protein response.

L3 ANSWER 17 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 2001:102422 BIOSIS
DN PREV200100102422
TI The double-stranded RNA-activated protein kinase PKR is dispensable for regulation of translation initiation in response to either calcium mobilization from the endoplasmic reticulum or essential amino acid starvation.
AU Kimball, Scot R. (1); Clemens, Michael J.; Tilleray, Vivienne J.; Wek, Ronald C.; Horetsky, Rick L. (1); Jefferson, Leonard S. (1)
CS (1) Department of Cellular and Molecular Physiology, College of Medicine, Pennsylvania State University, Hershey, PA, 17033 USA
SO Biochemical and Biophysical Research Communications, (January 12, 2001) Vol. 280, No. 1, pp. 293-300. print.
ISSN: 0006-291X.
DT Article
LA English
SL English
AB The alpha-subunit of eukaryotic initiation factor eIF2 is a preferred substrate for the double-stranded RNA-activated protein kinase, PKR. Phosphorylation of eIF2alpha converts the factor from a substrate into a competitive inhibitor of the guanine nucleotide exchange factor, eIF2B, leading to a decline in mRNA translation. Early studies provided evidence implicating PKR as the kinase that phosphorylates eIF2alpha under conditions of cell stress such as the accumulation of misfolded proteins in the lumen of the endoplasmic reticulum, i.e., the unfolded protein response (UPR). However, the recent identification of a transmicrosomal membrane eIF2alpha kinase, termed PEK or ***PERK*** , suggests that this kinase, and not PKR, might be the kinase that is activated by misfolded protein accumulation. Similarly, genetic studies in yeast provide compelling evidence that a kinase termed GCN2 phosphorylates eIF2alpha in response to amino acid deprivation. However, no direct evidence showing activation of the mammalian homologue of GCN2 by amino acid deprivation has been reported. In the present study, we find that in fibroblasts treated with agents that promote the UPR, protein synthesis is inhibited as a result of a decrease in eIF2B activity. Furthermore, the reduction in eIF2B activity is associated with enhanced phosphorylation of eIF2alpha. Importantly, the magnitude of the change in each parameter is identical in wildtype cells and in fibroblasts containing a chromosomal ***deletion*** in the PKR gene (PKR-KO cells). In a similar manner, we find that during amino acid deprivation the inhibition of protein synthesis and extent of increase in eIF2alpha phosphorylation are identical in wildtype and PKR-KO cells. Overall, the results show that PKR is not required for increased eIF2alpha phosphorylation or inhibition of protein synthesis under conditions promoting the UPR or in response to amino acid deprivation.

L3 ANSWER 18 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 2001:345080 BIOSIS
DN PREV200100345080
TI The unfolded protein response and Alzheimer's disease.
AU Imaizumi, Kazunori (1); Miyoshi, Ko; Katayama, Taiichi; Yoneda, Takunari; Taniguchi, Manabu; Kudo, Takashi; Tohyama, Masaya
CS (1) Division of Structural Cell Biology, Nara Institute of Science and Technology (NAIST), 8916-5, Takayama, Ikoma, Nara, 630-0101: imaizumi@bs.aist-nara.ac.jp Japan
SO Biochimica et Biophysica Acta, (31 May, 2001) Vol. 1536, No. 2-3, pp. 85-96. print.
ISSN: 0006-3002.
DT General Review
LA English
SL English
AB ***Disruption*** of calcium homeostasis, inhibition of protein glycosylation, and reduction of disulfide bonds provoke accumulation of unfolded protein in the endoplasmic reticulum (ER), and are therefore a type of 'ER stress'. Normal cells respond to ER stress by increasing transcription of genes encoding ER-resident chaperones such as GRP78/BiP, GRP94 and protein disulfide isomerase to facilitate protein folding. This induction system is termed the unfolded protein response. Familial Alzheimer's disease-linked presenilin-1 (PS1) mutation downregulates the unfolded protein response and leads to vulnerability to ER stress. The mechanisms by which mutant PS1 affects the ER stress response are attributed to the inhibited activation of ER stress transducers such as IRE1, ***PERK*** and ATF6.

L3 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2000:742294 CAPLUS
DN 133:317536
TI Tissue-specific and pathogen-specific toxic agents and ribozymes
IN Norris, James; Clawson, Gary; Westwater, Caroline; Schofield, David; Schmidt, Michael; Hoel, Brian; Dolan, Joseph; Pan, Wei-Hua
PA Musc Foundation for Research Development, USA; Penn State University
SO PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000061804	A1	20001019	WO 2000-US10229	20000414
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6271359	B1	20010807	US 1999-291902	19990414
EP 1169480	A1	20020109	EP 2000-922262	20000414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002541822	T2	20021210	JP 2000-611726	20000414
PRAI US 1999-291902	A	19990414		
US 2000-548449	A	20000413		
WO 2000-US10229	W	20000414		

AB The present invention relates to the discovery, identification and characterization of toxic agents which are lethal to pathogens and methods for targeting such toxic agents to a pathogen or pathogen infected cells to treat and/or eradicate the infection. In particular, the present invention relates to toxic agents which target bacteria at different stages of the bacterial life cycle, which are delivered alone or in combination to bacteria or bacteria-infected cells. The invention relates to toxic agents which are lethal to diseased cells and methods for targeting such toxic agents to a diseased cell to treat and/or eradicate the disease. The present invention relates to promoter elements which are pathogen-specific or tissue-specific and the use of such promoter elements to achieve pathogen-specific or tissue-specific expression of the toxic agent(s) and/or ribozyme(s) of the present invention. Specifically, the invention relates to the delivery of one or more toxic gene products, antisense RNAs, or ribozymes, or combination thereof. The invention provides a novel system by which multiple pathogenic targets may be simultaneously targeted to cause the death of a pathogen, or cell infected with a pathogen. Further, the invention has important implications in the eradication of drug-resistant bacterium and bacterial pathogens. The invention provides a novel system by which multiple targets may be simultaneously targeted to cause the death of a diseased cell. The invention has important implications in the eradication of drug-resistant pathogens (such as antibiotic resistant bacteria) and drug-resistant diseased cells (such as drug-resistant cancer cells).
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 2000:190316 BIOSIS
DN PREV200000190316
TI Pancreatic eukaryotic initiation factor-2alpha kinase (PEK) homologues in humans, Drosophila melanogaster and Caenorhabditis elegans that mediate translational control in response to endoplasmic reticulum stress.
AU Sood, Ruchira; Porter, Amy C.; Ma, Kun; Quilliam, Lawrence A.; Wek, Ronald C. (1)
CS (1) Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, 46202 USA
SO Biochemical Journal, (March, 2000) Vol. 346, No. 2, pp. 281-293.
ISSN: 0264-6021.
DT Article
LA English
SL English

AB In response to different cellular stresses, a family of protein kinases regulates translation by phosphorylation of the alpha subunit of eukaryotic initiation factor-2 (eIF-2alpha). Recently, we identified a new family member, pancreatic eIF-2alpha kinase (PEK) from rat pancreas. PEK, also referred to as RNA-dependent protein kinase (PKR)-like endoplasmic reticulum (ER) kinase (***PERK***) is a transmembrane protein implicated in translational control in response to stresses that impair protein folding in the ER. In this study, we identified and characterized PEK homologues from humans, Drosophila melanogaster and Caenorhabditis elegans. Expression of human PEK mRNA was found in over 50 different tissues examined, with highest levels in secretory tissues. In mammalian cells subjected to ER stress, we found that elevated eIF-2alpha phosphorylation was coincident with increased PEK autophosphorylation and eIF-2alpha kinase activity. Activation of PEK was abolished by ***deletion*** of PEK N-terminal sequences located in the ER lumen. To address the role of C. elegans PEK in translational control, we expressed this kinase in yeast and found that it inhibits growth by hyperphosphorylation of eIF-2alpha and inhibition of eIF-2B. Furthermore, we found that vaccinia virus K3L protein, an inhibitor of the eIF-2alpha kinase PKR involved in an anti-viral defence pathway, also reduced PEK activity. These results suggest that decreased translation initiation by PEK during ER stress may provide the cell with an opportunity to remedy the folding problem prior to introducing newly synthesized proteins into the secretory pathway.

L3 ANSWER 21 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 1998:208261 BIOSIS
DN PREV199800208261
TI The type I activin receptor ActRIB is required for egg cylinder organization and gastrulation in the mouse.
AU Gu, Zhenyu; Nomura, Masatoshi; Simpson, Brenda B.; Lei, Hong; Feijen, Alie; Van Den Eijnden-Van Raaij, Janny; Donahoe, Patrick K.; Li, En (1)
CS (1) Cardiovasc. Res. Cent., Massachusetts Gen. Hosp. East, Dep. Med., Harvard Med. Sch., Charlestown, MA 02129 USA
SO Genes & Development, (March 15, 1998) Vol. 12, No. 6, pp. 844-857. ISSN: 0890-9369.
DT Article
LA English
AB ActRIB is a ***type*** ***I*** ***transmembrane*** ***serine*** / ***threonine*** ***kinase*** receptor that has been shown to form heteromeric complexes with the type II activin receptors to mediate activin signal. To investigate the function of ActRIB in mammalian development, we generated ActRIB- ***deficient*** ES cell lines and mice by gene targeting. Analysis of the ActRIB-/- embryos showed that the epiblast and the extraembryonic ectoderm were disorganized, resulting in ***disruption*** and developmental arrest of the egg cylinder before gastrulation. To assess the function of ActRIB in mesoderm formation and gastrulation, chimera analysis was conducted. We found that ActRIB-/- ES cells injected into wild-type blastocysts were able to contribute to the mesoderm in chimeric embryos, suggesting that ActRIB is not required for mesoderm formation. Primitive streak formation, however, was impaired in chimeras when ActRIB-/- cells contributed highly to the epiblast. Further, chimeras generated by injection of wild-type ES cells into ActRIB-/- blastocysts formed relatively normal extraembryonic tissues, but the embryo proper developed poorly probably resulting from severe gastrulation defect. These results provide genetic evidence that ActRIB functions in both epiblast and extraembryonic cells to mediate signals that are required for egg cylinder organization and gastrulation.

L3 ANSWER 22 OF 24 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 1985:411850 BIOSIS
DN BA80:81842
TI SLIT-LAMP MICROSCOPIC APPEARANCE OF CORNEAL WOUND HEALING AFTER RADIAL
KERATOTOMY.
AU WARING G O III; STEINBERG E B; WILSON L A
CS EMORY CLINIC, 1365 CLIFTON ROAD N.E., ATLANTA, GA. 30322.
SO AM J OPHTHALMOL, (1985) 100 (1), 218-224.
CODEN: AJOPAA. ISSN: 0002-9394.
FS BA; OLD
LA English
AB Radial keratotomy offers a unique opportunity to study corneal wound healing because the corneas are normal, the fine knife blades ***disrupt*** adjacent tissue minimally, no sutures are used, there is minimal inflammation, and few postoperative drugs are administered. Corneal wounds were studied with a slit-lamp microscope as they healed from 2 wk to three years after radial keratotomy in 84 eyes of 51 consecutive patients enrolled in the Prospective Evaluation of Radial Keratotomy (***PERK***) Study. One day after surgery, the incisions were surrounded by edema. At 2 wk, a dense, gray, diffusely marginated opacity occupied 0.1 mm on both sides of the incision. At 3 mo., the area adjacent to the incision was filled with discrete, fine, gray spicules that protruded at right angles from the incision. At 6 mo., the gray cloudiness had completely disappeared, and the individual spicules were more prominent. By 1 yr, the spicules were disappearing from the anterior portion of the incision and were concentrated primarily in the posterior part of the incisions. At 2 and 3 years, the incision scar was fainter and the spicules had disappeared from all but the deep posterior part of the wound. It is believed that these spicules correspond to the reorganization of the stroma along the edges of the corneal incision. The persistence of the spicules suggests that wound healing in radial keratotomy may not be complete > until 2 yr after surgery.

L3 ANSWER 23 OF 24 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 85225282 EMBASE
DN 1985225282
TI Training, leadership and group composition: A review of the crucial variables.
AU Salvendy J.T.
CS St. Michael's Hospital, Toronto, Ont. M5B 1W8, Canada
SO Group Analysis, (1985) 18/2 (132-147).
CODEN: GRANEQ
CY United Kingdom
DT Journal
FS 032 Psychiatry
017 Public Health, Social Medicine and Epidemiology
LA English
AB A number of ***deficiencies*** and misconceptions associated with the group therapeutic education and practice have been reviewed. The following recommendations and comments are made: The rules for training in group psychotherapy should be firmed up, and as much as feasible made uniform in the various centres. The medical model, while under considerable attack for other reasons, can serve to demonstrate how insistence on certain standards allows for cross-regional and cross-country comparison and evaluation of the level of expertise attained. The demographic composition of a group is often unnecessarily restricted by an unsubstantiated 'rule' or through the neglectful handling of the non-common member. Any new 'band-wagon' phenomenon in group psychotherapy should be evaluated carefully, to ascertain that the primary beneficiaries are indeed the patients, and that one is not creating another ***perk*** or innovation for the sake of the therapist(s).

L3 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 1973:490996 CAPLUS
DN 79:90996
TI Identification and correction of copper ***deficiency*** of Rhododendron simsi George Lindley Taber cuttings
AU Dickey, R. D.
CS Ornamental Hortic. Dep., Inst. Food Agric. Sci., Gainesville, FL, USA
SO Proceedings of the Florida State Horticultural Society (1973), Volume Date 1972, 85, 398-400
CODEN: PFSHA7; ISSN: 0097-1219
DT Journal
LA English
AB A nutritional disorder of rooted cuttings of George Lindley Taber azalea, similar in appearance to previously identified Cu ***deficiency*** of Formosa and Fielder's White azaleas, was obsd. in a Florida nursery in June, 1971. Cu ***deficiency*** visual symptoms appeared on young leaves and twigs growing from terminal portions of the rooted cuttings; leaves and shoot growth were reduced in size. Some of the leaves developed tip burn, got slightly rumpled and twisted, esp. at the tips, some of the leaves dropped prematurely, and twigs died back. Chlorosis developed over the entire surface of the leaves. This disorder of rooted cuttings of George Lindley Taber azalea was corrected by Cu-contg. fertilizers. Cu was applied at rates equiv. to 10, 25, or 50 lb CuSO4/acre. All plants receiving CuSO4 or ***Perk*** grew normally, where 42% of the untreated plants died. There was no difference in size and quality of plants treated with either CuSO4 or ***Perk*** fertilizer.

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NEWS 3 Apr 09 BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4 Apr 09 ZDB will be removed from STN
NEWS 5 Apr 19 US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6 Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available
NEWS 9 Jun 03 New e-mail delivery for search results now available
NEWS 10 Jun 10 MEDLINE Reload
NEWS 11 Jun 10 PCTFULL has been reloaded
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY
NEWS 15 Jul 30 NETFIRST to be removed from STN
NEWS 16 Aug 08 CANCERLIT reload
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18 Aug 08 NTIS has been reloaded and enhanced
NEWS 19 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20 Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21 Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22 Aug 26 Sequence searching in REGISTRY enhanced
NEWS 23 Sep 03 JAPIO has been reloaded and enhanced
NEWS 24 Sep 16 Experimental properties added to the REGISTRY file
NEWS 25 Sep 16 CA Section Thesaurus available in CAPLUS and CA
NEWS 26 Oct 01 CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27 Oct 21 EVENTLINE has been reloaded
NEWS 28 Oct 24 BEILSTEIN adds new search fields
NEWS 29 Oct 24 Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30 Oct 25 MEDLINE SDI run of October 8, 2002
NEWS 31 Nov 18 DKILIT has been renamed APOLLIT
NEWS 32 Nov 25 More calculated properties added to REGISTRY
NEWS 33 Dec 02 TIBKAT will be removed from STN
NEWS 34 Dec 04 CSA files on STN
NEWS 35 Dec 17 PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36 Dec 17 TOXCENTER enhanced with additional content
NEWS 37 Dec 17 Adis Clinical Trials Insight now available on STN
NEWS 38 Dec 30 ISMEC no longer available
NEWS 39 Jan 21 NUTRACEUT offering one free connect hour in February 2003
NEWS 40 Jan 21 PHARMAML offering one free connect hour in February 2003
NEWS 41 Jan 29 Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 42 Feb 13 CANCERLIT is no longer being updated
NEWS 43 Feb 24 METADEX enhancements
NEWS 44 Feb 24 PCTGEN now available on STN
NEWS 45 Feb 24 TEMA now available on STN
NEWS 46 Feb 26 NTIS now allows simultaneous left and right truncation
NEWS 47 Feb 26 PCTFULL now contains images
NEWS 48 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 49 Mar 19 APOLLIT offering free connect time in April 2003
NEWS 50 Mar 20 EVENTLINE will be removed from STN
NEWS 51 Mar 24 PATDPAFULL now available on STN
NEWS 52 Mar 24 Additional information for trade-named substances without structures available in REGISTRY
NEWS 53 Mar 24 Indexing from 1957 to 1966 added to records in CA/CAPLUS

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=> s PERK or PEK
L1 971 PERK OR PEK

=> s l1 and (transgen? or knockout or disrupt? or deficie? or delet?)
L2 53 L1 AND (TRANSGEN? OR KNOCKOUT OR DISRUPT? OR DEFICIE? OR DELET?)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 30 DUP REM L2 (23 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 30 ANSWERS - CONTINUE? Y/(N):y

L3 ANSWER 1 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2003:5349 CAPLUS
DN 138:50942
TI Improvement of Corynebacterium glutamicum amino acid production by site-directed ***deletion*** of pck (PEP carboxykinase) gene
IN Eikmanns, Bernhard; Riedel, Christian; Sahm, Hermann; Mockel, Bettina
PA Germany
SO U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U.S. Ser. No. 59,091.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003003548	A1	20030102	US 2002-138713	20020506
DE 19950409	A1	20010426	DE 1999-19950409	19991020
US 2002065403	A1	20020530	US 1999-455777	19991207
US 6420151	B1	20020716		

PRAI DE 1999-19950409 A 19991020
US 1999-455777 A3 19991207
US 2002-59091 A2 20020130
AB The invention relates to isolated nucleotide sequences from Coryneform bacteria which code for the pck gene encoding the enzyme phosphoenol pyruvate carboxykinase (PEP carboxykinase). The invention also relates a process for the fermentative prepn. of L-amino acids, in particular L-lysine, L-threonine, and L-glutamate by attenuation of the pck gene. Thus Corynebacterium glutamicum strains producing L-lysine, L-threonine, and L-glutamate were subjected to site-directed ***deletion*** of gene pck using plasmid pk19mobsacB.DELTA.pck. Isolated transconjugants demonstrated enhance fermentative prodn. the desired amino acids.

L3 ANSWER 2 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2003:128287 BIOSIS
DN PREV200300128287
TI Functional characterization of Drosophila melanogaster ***PERK*** eukaryotic initiation factor 2alpha (eIF2alpha) kinase.
AU Pomar, Natalia; Berlanga, Juan J.; Campuzano, Sonsoles; Hernandez, Greco; Elias, Monica; de Haro, Cesar (1)
CS (1) Centro de Biologia Molecular 'Severo Ochoa', Facultad de Ciencias, CSIC-UAM, Cantoblanco, Madrid, 28049, Spain: cdeharo@cbm.uam.es Spain
SO European Journal of Biochemistry, (January 2003, 2003) Vol. 270, No. 2, pp. 293-306. print.
ISSN: 0014-2956.
DT Article
LA English
AB Four distinct eukaryotic initiation factor 2alpha (eIF2alpha) kinases phosphorylate eIF2alpha at S51 and regulate protein synthesis in response to various environmental stresses. These are the hemin-regulated inhibitor (HRI), the interferon-inducible dsRNA-dependent kinase (PKR), the endoplasmic reticulum (ER)-resident kinase (***PERK***) and the GCN2 protein kinase. Whereas HRI and PKR appear to be restricted to mammalian cells, GCN2 and ***PERK*** seem to be widely distributed in eukaryotes. In this study, we have characterized the second eIF2alpha kinase found in Drosophila, a ***PERK*** homologue (DPERK). Expression of DPERK is developmentally regulated. During embryogenesis, DPERK expression becomes concentrated in the endodermal cells of the gut and in the germ line precursor cells. Recombinant wild-type DPERK, but not the inactive DPERK-K671R mutant, exhibited an autokinase activity, specifically phosphorylated Drosophila eIF2alpha at S50, and functionally replaced the endogenous Saccharomyces cerevisiae GCN2. The full length protein, when expressed in 293T cells, located in the ER-enriched fraction, and its subcellular localization changed with ***deletion*** of different N-terminal fragments. Kinase activity assays with these DPERK

deletion mutants suggested that DPERK localization facilitates its in vivo function. Similar to mammalian ***PERK*** , DPERK forms oligomers in vivo and DPERK activity appears to be regulated by ER stress. Furthermore, the stable complexes between wild-type DPERK and DPERK-K671R
mutant were mediated through the N terminus of the proteins and exhibited an in vitro eIF2alpha kinase activity.

L3 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:906548 CAPLUS
DN 138:290
TI Methods of screening test substances for treating or preventing diseases involving an oxidative stress
IN Ron, David; Harding, Heather P.
PA New York University, USA
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002095061	A1	20021128	WO 2002-US15766	20020517
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003008272	A1	20030109	US 2002-150759	20020517

PRAI US 2001-292054P P 20010518
AB The invention is directed to methods for identifying test substances useful for the prevention or treatment of diseases involving an oxidative stress. The methods involve screening assays, including high throughput screening techniques, in which the test substances are tested for their ability to promote resistance to oxidative stress by activating one or more points of the integrated stress response pathway, while not causing stress.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:51200 CAPLUS
DN 136:117362
TI Alphavirus vectors and virosomes with modified HIV genes for use as vaccines
IN Olmsted, Robert; Keith, Paula; Dryga, Sergey; Caley, Ian; Maughan, Maureen; Johnston, Robert; Davis, Nancy; Swanstrom, Ronald
PA Alphavax, Inc., USA; University of North Carolina at Chapel Hill
SO PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002003917	A2	20020117	WO 2001-US21701	20010709
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001073313	A5	20020121	AU 2001-73313	20010709

PRAI US 2000-216995P P 20000707
WO 2001-US21701 W 20010709
AB The present invention provides methods and compns. comprising a population of alphavirus replicon particles comprising two or more isolated nucleic acids selected from (1) an isolated nucleic acid encoding an env gene product or an immunogenic fragment thereof of a human immunodeficiency virus, (2) an isolated nucleic acid encoding a gag gene product or an immunogenic fragment thereof of a human immunodeficiency virus, wherein the gag gene product or immunogenic fragment thereof is modified to inhibit formation of virus-like particles contg. the gag gene product or the immunogenic fragment thereof and their release from a cell, and (3) an isolated nucleic acid encoding a pol gene product or an immunogenic fragment thereof of a human immunodeficiency virus, wherein the pol gene product or immunogenic fragment thereof is modified to inhibit integrase, Rnase H and/or reverse transcriptase activity, and wherein the nucleic acids are each contained within a sep. alphavirus replicon particle.

L3 ANSWER 5 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:638353 CAPLUS
DN 137:180792
TI ***Transgenic*** mice containing type I transmembrane ER-resident serine/threonine protein kinase gene ***PERK*** ***disruptions*** and their use as disease models and for screening for modulators
IN Allen, Keith D.; Wiles, Michael V.
PA USA
SO U.S. Pat. Appl. Publ., 34 pp., which which which
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002116730	A1	20020822	US 2001-5983	20011107

PRAI US 2000-246676P P 20001107
US 2001-311018P P 20010808
US 2001-324765P P 20010924
US 2001-326148P P 20010928
AB The present invention relates to ***transgenic*** animals, as well as compns. and methods relating to the characterization of gene function. Specifically, the present invention provides ***transgenic*** mice comprising a ***disruption*** in the ***PERK*** gene encoding a type I transmembrane endoplasmic reticulum-resident serine-threonine protein kinase, which is known to phosphorylate protein formation initiation factor eIF2-.alpha.. To investigate the role of ***PERK*** , ***disruptions*** in the ***PERK*** genes are produced by homologous recombination using 5' and 3' arms in a targeting construct. The ***transgenic*** mice exhibit seizure-like responses at a lower doses of Metrazol, relative to a wild-type mouse. Such ***transgenic*** mice are useful as models for disease and for identifying agents that modulate gene expression and gene function, and as potential treatments for various disease states and disease conditions.

L3 ANSWER 6 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:398652 BIOSIS
DN PREV200200398652
TI Dimerization and release of molecular chaperone inhibition facilitate activation of eukaryotic initiation factor-2 kinase in response to endoplasmic reticulum stress.
AU Ma, Kun; Vattem, Krishna M.; Wek, Ronald C. (1)
CS (1) Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, 46202: rwek@iupui.edu USA
SO Journal of Biological Chemistry, (May 24, 2002) Vol. 277, No. 21, pp. 18728-18735. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Phosphorylation of eukaryotic initiation factor-2 (eIF2) by pancreatic eIF2 kinase (***PEK***), induces a program of translational expression in response to accumulation of malfolded protein in the endoplasmic reticulum (ER). This study addresses the mechanisms activating ***PEK*** , also designated ***PERK*** or EIF2AK3. We describe the characterization of two regions in the ER luminal portion of the transmembrane ***PEK*** that carry out distinct functions in the regulation of this eIF2 kinase. The first region mediates oligomerization between ***PEK*** polypeptides, and ***deletion*** of this portion of ***PEK*** blocked induction of eIF2 kinase activity. The second characterized region of ***PEK*** facilitates interaction with ER chaperones. In the absence of stress, ***PEK*** associates with ER chaperones GRP78 (BiP) and GRP94, and this binding is released in response to ER stress. ER luminal sequences flanking the transmembrane domain are required for GRP78 interaction, and ***deletion*** of this portion of ***PEK*** led to its activation even in the absence of ER stress. These results suggest that this ER chaperone serves as a repressor of ***PEK*** activity, and release of ER chaperones from ***PEK*** when misfolded proteins accumulate in the ER induces gene expression required to enhance the protein folding capacity of the ER.

L3 ANSWER 7 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2003:71647 BIOSIS
DN PREV200300071647
TI Control of ***PERK*** eIF2alpha kinase activity by the endoplasmic reticulum stress-induced molecular chaperone P58IPK.
AU Yan, Wei (1); Frank, Christopher L.; Korth, Marcus J.; Sopher, Bryce L.; Novoa, Isabel; Ron, David; Katze, Michael G.
CS (1) Department of Microbiology, University of Washington, Box 358070, Seattle, WA, 98195-8070, USA: wyan96@u.washington.edu USA
SO Proceedings of the National Academy of Sciences of the United States of America, (December 10 2002) Vol. 99, No. 25, pp. 15920-15925. print.
ISSN: 0027-8424.
DT Article
LA English
AB P58IPK is an Hsp40 family member known to inhibit the interferon (IFN)-induced, double-stranded RNA-activated, eukaryotic initiation factor 2alpha (eIF2alpha) protein kinase R (PKR) by binding to its kinase domain. We find that the stress of unfolded proteins in the endoplasmic reticulum (ER) activates P58IPK gene transcription through an ER stress-response element in its promoter region. P58IPK interacts with and inhibits the PKR-like ER-localized eIF2alpha kinase ***PERK*** , which is normally activated during the ER-stress response to protect cells from ER stress by attenuating protein synthesis and reducing ER client protein load. Levels

of phosphorylated eIF2alpha were lower in ER-stressed P58IPK-overexpressing cells and were enhanced in P58IPK mutant cells. In the ER-stress response, PKR-like ER kinase (***PERK***)-mediated translational repression is transient and is followed by translational recovery and enhanced expression of genes that increase the capacity of the ER to process client proteins. The absence of P58IPK resulted in increased expression levels of two ER stress-inducible genes, BiP and Chop, consistent with the enhanced eIF2alpha phosphorylation in the P58IPK ***deletion*** cells. Our studies suggest that P58IPK induction during the ER-stress response represses ***PERK*** activity and plays a functional role in the expression of downstream markers of ***PERK*** activity in the later phase of the ER-stress response.

L3 ANSWER 8 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2002:564977 BIOSIS
DN PREV200200564977
TI Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase ***PERK*** and phosphorylation of the translation initiation factor eIF2alpha.
AU Koumenis, Constantinos (1); Naczki, Christine; Koritzinsky, Marianne; Rastani, Sally; Diehl, Alan; Sonenberg, Nahum; Koromilas, Antonis; Wouters, Bradly G.
CS (1) Departments of Radiation Oncology and Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC, 27157: ckoumeni@wfubmc.edu USA
SO Molecular and Cellular Biology, (November, 2002) Vol. 22, No. 21, pp. 7405-7416. http://mcb.asm.org/. print.
ISSN: 0270-7306.
DT Article
LA English
AB Hypoxia profoundly influences tumor development and response to therapy. While progress has been made in identifying individual gene products whose synthesis is altered under hypoxia, little is known about the mechanism by which hypoxia induces a global downregulation of protein synthesis. A critical step in the regulation of protein synthesis in response to stress is the phosphorylation of translation initiation factor eIF2alpha on Ser51, which leads to inhibition of new protein synthesis. Here we report that exposure of human diploid fibroblasts and transformed cells to hypoxia led to phosphorylation of eIF2alpha, a modification that was readily reversed upon reoxygenation. Expression of a transdominant, nonphosphorylatable mutant allele of eIF2alpha attenuated the repression of protein synthesis under hypoxia. The endoplasmic reticulum (ER)-resident eIF2alpha kinase ***PERK*** was hyperphosphorylated upon hypoxic stress, and overexpression of wild-type ***PERK*** increased the levels of hypoxia-induced phosphorylation of eIF2alpha. Cells stably expressing a dominant-negative ***PERK*** allele and mouse embryonic fibroblasts with a homozygous ***deletion*** of ***PERK*** exhibited attenuated phosphorylation of eIF2alpha and reduced inhibition of protein synthesis in response to hypoxia. ***PERK*** -/- mouse embryo fibroblasts failed to phosphorylate eIF2alpha and exhibited lower survival after prolonged exposure to hypoxia than did wild-type fibroblasts. These results indicate that adaptation of cells to hypoxic stress requires activation of ***PERK*** and phosphorylation of eIF2alpha and suggest that the mechanism of hypoxia-induced translational attenuation may be linked to ER stress and the unfolded-protein response.

L3 ANSWER 9 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2002:318997 BIOSIS
DN PREV200200318997
TI The ***PERK*** eukaryotic initiation factor 2alpha kinase is required for the development of the skeletal system, postnatal growth, and the function and viability of the pancreas.
AU Zhang, Peichuan; McGrath, Barbara; Li, Sheng'ai; Frank, Ami; Zambito, Frank; Reinert, Jamie; Gannon, Maureen; Ma, Kun; McNaughton, Kelly; Cavener, Douglas R. (1)
CS (1) Department of Biology, The Pennsylvania State University, 208 Mueller Lab, University Park, PA, 16802: drc9@psu.edu USA
SO Molecular and Cellular Biology, (June, 2002) Vol. 22, No. 11, pp. 3864-3874. http://mcb.asm.org/. print.
ISSN: 0270-7306.
DT Article
LA English
AB Phosphorylation of eukaryotic initiation factor 2alpha (eIF-2alpha) is typically associated with stress responses and causes a reduction in protein synthesis. However, we found high phosphorylated eIF-2alpha (eIF-2alpha(P)) levels in nonstressed pancreata of mice. Administration of glucose stimulated a rapid dephosphorylation of eIF-2alpha. Among the four eIF-2alpha kinases present in mammals, ***PERK*** is most highly expressed in the pancreas, suggesting that it may be responsible for the high eIF-2alpha(P) levels found therein. We describe a ***Perk*** ***knockout*** mutation in mice. Pancreata of ***Perk*** -/- mice are morphologically and functionally normal at birth, but the islets of Langerhans progressively degenerate, resulting in loss of insulin-secreting beta cells and development of diabetes mellitus, followed later by loss of glucagon-secreting alpha cells. The exocrine pancreas exhibits a reduction in the synthesis of several major digestive enzymes and succumbs to massive apoptosis after the fourth postnatal week. ***Perk*** -/- mice also exhibit skeletal dysplasias at birth and postnatal growth retardation. Skeletal defects include ***deficient*** mineralization, osteoporosis, and abnormal compact bone development. The skeletal and pancreatic defects are associated with defects in the rough endoplasmic reticulum of the major secretory cells that comprise the skeletal system and pancreas. The skeletal, pancreatic, and growth defects are similar to those seen in human Wolcott-Rallison syndrome.

L3 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:521732 CAPLUS
DN 137:230749
TI Loss of kinase activity in a patient with Wolcott-Rallison syndrome caused by a novel mutation in the EIF2AK3 gene
AU Biason-Lauber, Anna; Lang-Muritano, Mariarosaria; Vaccaro, Tindara; Schoenle, Eugen J.
CS Division of Pediatric Endocrinology/Diabetology, University Children's Hospital, Zurich, 8032, Switz.
SO Diabetes (2002), 51(7), 2301-2305
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
AB Wolcott-Rallison syndrome (WRS) is an autosomal recessive disorder characterized by neonatal or early infancy type 1 diabetes, epiphyseal dysplasia, and growth retardation. Mutations in the EIF2AK3 gene, encoding the eukaryotic initiation factor 2.alpha.-kinase 3 (EIF2AK3), have been found in WRS patients. Here we describe a girl who came to our attention at 2 mo of age with severe hypertonic dehydration and diabetic ketoacidosis. A diagnosis of type 1 diabetes was made and insulin treatment initiated. Growth retardation and microcephaly were also present. Anti-islet cell autoantibodies were neg., and mitochondrial diabetes was excluded. Imaging revealed a hypoplastic pancreas and typical signs of spondylo-epiphyseal dysplasia. The diagnosis of WRS was therefore made at age 5 yr. Sequencing anal. of her EIF2AK3 gene revealed the presence of a homozygous T to C exchange in exon 13 leading to the missense serine 877 proline mutation. The mutated kinase, although it partly retains the ability of autophosphorylation, is unable to phosphorylate its natural substrate, eukaryotic initiation factor 2.alpha. (eIF2.alpha.). This is the first case in which the pathophysiol. role of EIF2AK3 ***deficiency*** in WRS is confirmed at the mol. level. Our data demonstrate that EIF2AK3 kinase activity is essential for pancreas islet function and bone development in humans, and we suggest EIF2AK3 as a possible target for therapeutic intervention in diabetes.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:369670 BIOSIS
DN PREV200200369670
TI The cellular response to accumulation of unfolded proteins in the endoplasmic reticulum.
AU Kaufman, Randal J. (1)
CS (1) Biological Chemistry, Med School, HHMI/Univ.Mich, 1150 W Medical Center Drive, Ann Arbor, MI, 48109-0560 USA
SO FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A891. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DT Conference
LA English
AB The unfolded protein response (UPR) is an adaptive program activated by the accumulation of unfolded proteins in the endoplasmic reticulum (ER). In higher eukaryotes, there exist three ER-localized proximal sensors of the UPR; IRE1, ATF6, and ***PERK*** . On signaling the UPR, IRE1 protein kinase activates its endoribonuclease function to initiate a splicing reaction on an mRNA encoding a basic leucine zipper transcription factor that is sufficient for UPR transcriptional induction. In addition, the UPR induces proteolytic cleavage of the ER transmembrane activating transcription factor ATF6 to yield a cytosolic fragment that migrates to the nucleus and is required to activate transcription of the ER stress response genes. Activation of the UPR also results in a transient translation inhibition mediated by ***PERK*** , a protein kinase that phosphorylates the alpha subunit of the eukaryotic translation initiation factor 2 (eIF2a) on residue Ser51. Therefore, activation of ***PERK*** limits the amount of protein that requires folding under conditions of ER stress. Interestingly, this translational control is also required for maximal transcriptional activation of the ER stress response genes. We have studied the role of these individual pathways by analysis of genetic ***deficiencies*** in murine and C. elegans species in vivo. The results support that all three pathways are not only required for survival upon ER stress, but are also essential for development.

L3 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:375215 CAPLUS
DN 137:181405
TI RNA-dependent protein kinases
AU Petryshyn, Raymond A.; Nekhai, Sergie; Perez-Albuerne, Evelio D.
CS National Cancer Institute, Bethesda, MD, USA
SO Endocrine Updates (2002), 16(RNA Binding Proteins), 175-191
CODEN: ECUDF4; ISSN: 1566-0729
PB Kluwer Academic Publishers
DT Journal; General Review

LA English
AB A review. RNA mols. conduct various functions in living organisms by interacting with other biol. mols. The recognition of RNA mols., usually by proteins, is often dependent on the shape into which the RNA folds, rather than on any specific nucleotide sequence. This review focuses on double-stranded RNA (dsRNA) dependent protein kinase (PKR), which phosphorylates the .alpha. subunit of eukaryotic initiation factor-2 (eIF-2.alpha.). PKR contains 2 amino acid sequence motifs called dsRNA-binding motifs (DRBM) that allow binding to dsRNA and subsequently convert the protein from a latent to an active serine/threonine protein kinase. PKR is the only known kinase that depends on dsRNA for activation, although 2 closely related eIF-2.alpha. kinases, pancreatic eIF-2.alpha. kinase (***PEK***) and PKR-like endoplasmic reticulum kinase (***PERK***), have been described. PKR presents a unique paradigm for studying RNA:protein interaction because its activity depends on binding to dsRNA but not DNA, single-stranded RNA, or RNA:DNA hybrids. Well-known for mediating the antiviral effects of interferons (IFNs), PKR is also implicated in regulating cell differentiation, signal transduction, and in eliciting apoptosis in response to various stress induction agents. Although the protein is ubiquitous in cells, PKR activity is suppressed during cell proliferation and in tumor cells, suggesting a role for the kinase in the regulation of cell proliferation. This review summarizes the viral and cellular proteins and dsRNAs that activate and inhibit PKR, and the most recent findings in PKR ***knockout*** mice.
RE.CNT 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:152848 CAPLUS
DN 134:218920
TI Brassica wounding- and pathogen-inducible proline-rich extensin-like receptor kinase PERK1 gene and ***transgenic*** plants expressing it
IN Goring, Daphne; Silva, Nancy
PA Can.
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001014563	A1	20010301	WO 2000-CA966	20000818

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-149466P P 19990819
US 1999-159122P P 19991013
AB The invention includes ***PERK*** (proline-rich extensin-like receptor kinase) nucleic acid mols. and polypeptides. A receptor-like protein kinase designated PERK1 (proline-rich extension-like receptor kinase 1) was isolated from an 8-pistil cDNA library of Brassica napus. The deduced PERK1 protein is comprised of a cytoplasmic domain that contains all of the conserved amino acids prevalent among serine/threonine kinases, a transmembrane domain and an extracellular domain with sequence similarity to the extensin family of plant cell wall proteins. Northern blot anal. demonstrated that PERK1 mRNA accumulated rapidly in leaf and stem tissue of B.napus in response to wounding and treatment with salicylic acid. In contrast, no significant accumulation of PERK1 mRNA was detected following treatment with Me jasmonate. The rapidity of PERK1 mRNA accumulation in response to these treatments shows a role in plant defense signaling.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:297585 CAPLUS
DN 134:321603
TI Isolation of nucleotide sequences encoding PEP carboxykinase
IN Eikmanns, Bernhard; Riedel, Christian; Sahm, Hermann; Mockel, Bettina
PA Degussa-Huls A.-G., Germany; Forschungszentrum Julich G.m.b.H.
SO Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1094111	A2	20010425	EP 2000-121715	20001005
EP 1094111	A3	20010718		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

DE 19950409	A1	20010426	DE 1999-19950409	19991020
JP 2001149086	A2	20010605	JP 2000-316432	20001017
BR 2000004957	A	20010529	BR 2000-4957	20001020
CN 1308125	A	20010815	CN 2000-129864	20001020

PRAI DE 1999-19950409 A 19991020
AB A polynucleotide sequence that is 70% identical to the polynucleotide sequence that encodes PEP carboxykinase was isolated from Corynebacterium glutamicum by cloning E. coli strain DSM 13047 vector pK19mobsacB.DELTA.pck carrying the pck gene. Expression of the pck gene in Corynebacterium glutamicum increased lysine and threonine yields.

L3 ANSWER 15 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 2002:190693 BIOSIS
DN PREV200200190693
TI Disturbed activation of endoplasmic reticulum stress transducers by familial Alzheimer's disease-linked presenilin-1 mutations.
AU Katayama, Taiichi; Imaizumi, Kazunori (1); Honda, Akiko; Yoneda, Takunari; Kudo, Takashi; Takeda, Masatoshi; Mori, Kazutoshi; Rozmahel, Richard; Fraser, Paul; St. George-Hyslop, Peter; Tohyama, Masaya
CS (1) Division of Structural Cell Biology, Nara Institute of Science and Technology (NAIST), 8916-5 Takayama, Ikoma, Nara, 630-0101: imaizumi@bs.aist-nara.ac.jp Japan
SO Journal of Biological Chemistry, (November 16, 2001) Vol. 276, No. 46, pp. 43446-43454. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Recent studies have shown independently that presenilin-1 (PS1) null mutants and familial Alzheimer's disease (FAD)-linked mutants should both down-regulate signaling of the unfolded protein response (UPR). However, it is difficult to accept that both mutants possess the same effects on the UPR. Furthermore, contrary to these observations, neither loss of PS1 and PS2 function nor expression of FAD-linked PS1 mutants were reported to have a discernable impact on the UPR. Therefore, re-examination and detailed analyses are needed to clarify the relationship between PS1 function and UPR signaling. Here, we report that PS1/PS2 null and dominant negative PS1 mutants, which are mutated at aspartate residue 257 or 385, did not affect signaling of the UPR. In contrast, FAD-linked PS1 mutants were confirmed to disturb UPR signaling by inhibiting activation of both Ire1alpha and ATF6, both of which are endoplasmic reticulum (ER) stress transducers in the UPR. Furthermore, PS1 mutants also disturbed activation of ***PERK*** (PKR-like ER kinase), which plays a crucial role in inhibiting translation during ER stress. Taken together, these observations suggested that PS1 mutations could affect signaling pathways controlled by each of the respective ER-stress transducers, possibly through a gain-of-function.

L3 ANSWER 16 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 2001:235047 BIOSIS
DN PREV200100235047
TI IRF3 and IRF7 phosphorylation in virus-infected cells does not require double-stranded RNA-dependent protein kinase R or IkappaB kinase but is blocked by vaccinia virus E3L protein.
AU Smith, Eric J.; Marie, Isabelle; Prakash, Arun; Garcia-Sastre, Adolfo; Levy, David E. (1)
CS (1) Dept. of Pathology, New York University School of Medicine, 550 First Ave., New York, NY, 10016: levyd01@med.nyu.edu USA
SO Journal of Biological Chemistry, (March 23, 2001) Vol. 276, No. 12, pp. 8951-8957. print.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB Induction of interferon-alpha (IFNalpha) gene expression in virus-infected cells requires phosphorylation-induced activation of the transcription factors IRF3 and IRF7. However, the kinase(s) that targets these proteins has not been identified. Using a combined pharmacological and genetic approach, we found that none of the kinases tested was responsible for IRF phosphorylation in cells infected with Newcastle disease virus (NDV). Although the broad-spectrum kinase inhibitor staurosporine potently blocked IRF3 and -7 phosphorylation, inhibitors for protein kinase-C, protein kinase A, MEK, SAPK, IKK, and protein kinase R (PKR) were without effect. Both IkappaB kinase and PKR have been implicated in IFN induction, but cells genetically ***deficient*** in IkappaB kinase, PKR, or the PKR-related genes ***PERK*** , IRE1, or GCN2 retained the ability to phosphorylate IRF7 and induce IFNalpha. Interestingly, PKR mutant cells were defective for response to double-stranded (ds) RNA but not to virus infection, suggesting that dsRNA is not the only activating viral component. Consistent with this notion, protein synthesis was required for IRF7 phosphorylation in virus-infected cells, and the kinetics of phosphorylation and viral protein production were similar. Despite evidence for a lack of involvement of dsrna and PKR, vaccinia virus E3L protein, a dsRNA-binding protein capable of inhibiting PKR, was an effective IRF3 and -7 phosphorylation inhibitor. These results suggest that a novel cellular protein that is activated by viral products in addition to dsrna and is sensitive to E3L inhibition is responsible for IRF activation and reveal a novel mechanism for the anti-IFN effect of E3L distinct from its inhibition of PKR.

L3 ANSWER 17 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 2001:471247 BIOSIS

DN PREV200100471247
TI Taurine prevents the decrease in expression and secretion of extracellular superoxide dismutase induced by homocysteine: Amelioration of homocysteine-induced endoplasmic reticulum stress by taurine.
AU Nonaka, Hidemi; Tsujino, Takeshi (1); Watari, Yasuhiro; Emoto, Noriaki; Yokoyama, Mitsuhiro
CS (1) Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki, Chuo, Kobe, 650-0017: hidemin@med.kobe-u.ac.jp Japan
SO Circulation, (September 4, 2001) Vol. 104, No. 10, pp. 1165-1170. print. ISSN: 0009-7322.
DT Article
LA English
SL English
AB Background: Hyperhomocysteinemia is an independent risk factor for atherosclerosis. Homocysteine has been shown to induce endoplasmic reticulum (ER) stress in vascular endothelial cells. ER stress is a condition in which glycoprotein trafficking is ***disrupted*** and unfolded proteins accumulate in the ER. ER molecular chaperons, such as GRP78, are induced and an ER resident kinase, ***PERK*** , is activated when cells are subjected to ER stress. Conversely, taurine is reported to have antiatherogenic effects by unknown mechanisms. To elucidate the mechanisms by which homocysteine induces atherosclerosis and taurine prevents it, we examined whether homocysteine and taurine affect the expression and secretion of extracellular superoxide dismutase (EC-SOD), a glycoprotein secreted from vascular smooth muscle cells (VSMCs) that protects the vascular wall from oxidative stress. Methods and Results: We assessed the expression of EC-SOD and GRP78 mRNA in cultured rat VSMCs by Northern blot analysis. The EC-SOD protein secreted into the culture medium was examined by Western blot analysis. Homocysteine (5 mmol/L) and other ER stress inducers, including A23187, were found to decrease EC-SOD mRNA expression and protein secretion. Furthermore, they upregulated GRP78 MRNA expression and activated ***PERK*** . Taurine (0.5 to 10 mmol/L), conversely, prevented these actions induced by homocysteine. Conclusions: Homocysteine induces ER stress and reduces the secretion and expression of EC-SOD in VSMCs, leading to increased oxidative stress in the vascular wall. Taurine restores the secretion and expression of EC-SOD by ameliorating ER stress induced by homocysteine.

L3 ANSWER 18 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002132258 EMBASE
TI Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2.alpha..
AU Novoa I.; Zeng H.; Harding H.P.; Ron D.
CS D. Ron, New York University Medical Center, 540 First Ave., New York, NY 10016, United States. ron@saturn.med.nyu.edu
SO Journal of Cell Biology, (25 May 2001) 153/5 (1011-1021). Refs: 42
ISSN: 0021-9525 CODEN: JCLBA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB Phosphorylation of the .alpha. subunit of eukaryotic translation initiation factor 2 (eIF2.alpha.) on serine 51 integrates general translation repression with activation of stress-inducible genes such as ATF4, CHOP, and BiP in the unfolded protein response. We sought to identify new genes active in this phospho-eIF2.alpha.-dependent signaling pathway by screening a library of recombinant retroviruses for clones that inhibit the expression of a CHOP::GFP reporter. A retrovirus encoding the COOH terminus of growth arrest and DNA damage gene (GADD)34, also known as MYD116 (Fornace, A.J., D.W. Neibert, M.C. Hollander, J.D. Luethy, M. Papathanasiou, J. Fragoli, and N.J. Holbrook. 1989. Mol. Cell. Biol. 9:4196-4203; Lord K.A., B. Hoffman-Lieberman, and D.A. Lieberman. 1990. Nucleic Acid Res. 18:2823), was isolated and found to attenuate CHOP (also known as GADD153) activation by both protein malfolding in the endoplasmic reticulum, and amino acid deprivation. Despite normal activity of the cognate stress-inducible eIF2.alpha. kinases ***PERK*** (also known as ***PEK***) and GCN2, phospho-eIF2.alpha. levels were markedly diminished in GADD34-overexpressing cells. GADD34 formed a complex with the catalytic subunit of protein phosphatase 1 (PP1c) that specifically promoted the dephosphorylation of eIF2.alpha. in vitro. Mutations that interfered with the interaction with PP1c prevented the dephosphorylation of eIF2.alpha. and blocked attenuation of CHOP by GADD34. Expression of GADD34 is stress dependent, and was absent in ***PERK*** (-/-) and GCN2(-/-) cells. These findings implicate GADD34-mediated dephosphorylation of eIF2.alpha. in a negative feedback loop that inhibits stress-induced gene expression, and that might promote recovery from translational inhibition in the unfolded protein response.

L3 ANSWER 19 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 2001:102422 BIOSIS
DN PREV200100102422
TI The double-stranded RNA-activated protein kinase PKR is dispensable for regulation of translation initiation in response to either calcium mobilization from the endoplasmic reticulum or essential amino acid starvation.
AU Kimball, Scot R. (1); Clemens, Michael J.; Tilleray, Vivienne J.; Wek, Ronald C.; Horetsky, Rick L. (1); Jefferson, Leonard S. (1)
CS (1) Department of Cellular and Molecular Physiology, College of Medicine, Pennsylvania State University, Hershey, PA, 17033 USA
SO Biochemical and Biophysical Research Communications, (January 12, 2001) Vol. 280, No. 1, pp. 293-300. print.
ISSN: 0006-291X.
DT Article
LA English
SL English
AB The alpha-subunit of eukaryotic initiation factor eIF2 is a preferred substrate for the double-stranded RNA-activated protein kinase, PKR. Phosphorylation of eIF2alpha converts the factor from a substrate into a competitive inhibitor of the guanine nucleotide exchange factor, eIF2B, leading to a decline in mRNA translation. Early studies provided evidence implicating PKR as the kinase that phosphorylates eIF2alpha under conditions of cell stress such as the accumulation of misfolded proteins in the lumen of the endoplasmic reticulum, i.e., the unfolded protein response (UPR). However, the recent identification of a transmicrosomal membrane eIF2alpha kinase, termed ***PEK*** or ***PERK*** , suggests that this kinase, and not PKR, might be the kinase that is activated by misfolded protein accumulation. Similarly, genetic studies in yeast provide compelling evidence that a kinase termed GCN2 phosphorylates eIF2alpha in response to amino acid deprivation. However, no direct evidence showing activation of the mammalian homologue of GCN2 by amino acid deprivation has been reported. In the present study, we find that in fibroblasts treated with agents that promote the UPR, protein synthesis is inhibited as a result of a decrease in eIF2B activity. Furthermore, the reduction in eIF2B activity is associated with enhanced phosphorylation of eIF2alpha. Importantly, the magnitude of the change in each parameter is identical in wildtype cells and in fibroblasts containing a chromosomal ***deletion*** in the PKR gene (PKR-KO cells). In a similar manner, we find that during amino acid deprivation the inhibition of protein synthesis and extent of increase in eIF2alpha phosphorylation are identical in wildtype and PKR-KO cells. Overall, the results show that PKR is not required for increased eIF2alpha phosphorylation or inhibition of protein synthesis under conditions promoting the UPR or in response to amino acid deprivation.

L3 ANSWER 20 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 2001:345080 BIOSIS
DN PREV200100345080
TI The unfolded protein response and Alzheimer's disease.
AU Imaizumi, Kazunori (1); Miyoshi, Ko; Katayama, Taiichi; Yoneda, Takunari; Taniguchi, Manabu; Kudo, Takashi; Tohyama, Masaya
CS (1) Division of Structural Cell Biology, Nara Institute of Science and Technology (NAIST), 8916-5, Takayama, Ikoma, Nara, 630-0101: imaizumi@bs.aist-nara.ac.jp Japan
SO Biochimica et Biophysica Acta, (31 May, 2001) Vol. 1536, No. 2-3, pp. 85-96. print.
ISSN: 0006-3002.
DT General Review
LA English
SL English
AB ***Disruption*** of calcium homeostasis, inhibition of protein glycosylation, and reduction of disulfide bonds provoke accumulation of unfolded protein in the endoplasmic reticulum (ER), and are therefore a type of 'ER stress'. Normal cells respond to ER stress by increasing transcription of genes encoding ER-resident chaperones such as GRP78/BiP, GRP94 and protein disulfide isomerase to facilitate protein folding. This induction system is termed the unfolded protein response. Familial Alzheimer's disease-linked presenilin-1 (PS1) mutation downregulates the unfolded protein response and leads to vulnerability to ER stress. The mechanisms by which mutant PS1 affects the ER stress response are attributed to the inhibited activation of ER stress transducers such as IRE1, ***PERK*** and ATF6.

L3 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:155523 CAPLUS
DN 136:180542
TI Isolation and characterization of multi copy suppressor of calcineurin ***deletion*** of fission yeast
AU Maekawa, Katsuhide; Kita, Ayako; Itoh, Yuumi; Sugiura, Reiko
CS Dep. Pharmacol., Kobe Univ. Sch. Med., Kobe, Japan
SO Kobe Daigaku Igakubu Kiyo (2001), 62(1,2), 11-16
CODEN: KDIKAX; ISSN: 0075-6431
PB Kobe Daigaku Igakubu
DT Journal
LA Japanese
AB Calcineurin is a conserved Ca2+/calmodulin-dependent protein phosphatase that plays a crit. role in Ca2+-mediated signaling in eucaryotic cells. In fission yeast a calcineurin homolog (Ppb 1) is required for cytokinesis and for chloride ion homeostasis but is not essential for cell viability. To identify genes the product of which interact calcineurin, we isolated multicopy plasmids that suppressed the Cl-sensitive growth defect of ppb 1. We identified four genes, three of which are previously identified genes-ppb1+, pmp1+, and ***pek*** 1+-with one novel gene, which has been designated msc1+ (multicopy suppressor of calcineurin ***deletion***). The msc1+ gene contains an open reading frame (ORF), encoding a novel evolutionarily highly conserved protein with the RNA-interacting KH motif. We also found that Cl-sensitive growth defect of calcineurin ***deletion*** was exacerbated when combined with msc1+

gene ***deletion*** . Together, these results suggest that Msc1 is likely to have a role in RNA metab., thereby suppressing calcineurin ***deletion*** phenotypes.

L3 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:742294 CAPLUS
DN 133:317536
TI Tissue-specific and pathogen-specific toxic agents and ribozymes
IN Norris, James; Clawson, Gary; Westwater, Caroline; Schofield, David; Schmidt, Michael; Hoel, Brian; Dolan, Joseph; Pan, Wei-Hua
PA Musc Foundation for Research Development, USA; Penn State University
SO PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000061804	A1	20001019	WO 2000-US10229	20000414
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6271359	B1	20010807	US 1999-291902	19990414
EP 1169480	A1	20020109	EP 2000-922262	20000414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002541822	T2	20021210	JP 2000-611726	20000414
PRAI US 1999-291902	A	19990414		
US 2000-548449	A	20000413		
WO 2000-US10229	W	20000414		

AB The present invention relates to the discovery, identification and characterization of toxic agents which are lethal to pathogens and methods for targeting such toxic agents to a pathogen or pathogen infected cells to treat and/or eradicate the infection. In particular, the present invention relates to toxic agents which target bacteria at different stages of the bacterial life cycle, which are delivered alone or in combination to bacteria or bacteria-infected cells. The invention relates to toxic agents which are lethal to diseased cells and methods for targeting such toxic agents to a diseased cell to treat and/or eradicate the disease. The present invention relates to promoter elements which are pathogen-specific or tissue-specific and the use of such promoter elements to achieve pathogen-specific or tissue-specific expression of the toxic agent(s) and/or ribozyme(s) of the present invention. Specifically, the invention relates to the delivery of one or more toxic gene products, antisense RNAs, or ribozymes, or combination thereof. The invention provides a novel system by which multiple pathogenic targets may be simultaneously targeted to cause the death of a pathogen, or cell infected with a pathogen. Further, the invention has important implications in the eradication of drug-resistant bacterium and bacterial pathogens. The invention provides a novel system by which multiple targets may be simultaneously targeted to cause the death of a diseased cell. The invention has important implications in the eradication of drug-resistant pathogens (such as antibiotic resistant bacteria) and drug-resistant diseased cells (such as drug-resistant cancer cells).
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 2000:190316 BIOSIS
DN PREV200000190316
TI Pancreatic eukaryotic initiation factor-2alpha kinase (***PEK***) homologues in humans, Drosophila melanogaster and Caenorhabditis elegans that mediate translational control in response to endoplasmic reticulum stress.
AU Sood, Ruchira; Porter, Amy C.; Ma, Kun; Quilliam, Lawrence A.; Wek, Ronald C. (1)
CS (1) Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, 46202 USA
SO Biochemical Journal, (March, 2000) Vol. 346, No. 2, pp. 281-293. ISSN: 0264-6021.
DT Article
LA English
SL English
AB In response to different cellular stresses, a family of protein kinases regulates translation by phosphorylation of the alpha subunit of eukaryotic initiation factor-2 (eIF-2alpha). Recently, we identified a new family member, pancreatic eIF-2alpha kinase (***PEK***) from rat pancreas. ***PEK*** , also referred to as RNA-dependent protein kinase (PKR)-like endoplasmic reticulum (ER) kinase (***PERK***) is a transmembrane protein implicated in translational control in response to stresses that impair protein folding in the ER. In this study, we identified and characterized ***PEK*** homologues from humans, Drosophila melanogaster and Caenorhabditis elegans. Expression of human ***PEK*** mRNA was found in over 50 different tissues examined, with highest levels in secretory tissues. In mammalian cells subjected to ER stress, we found that elevated eIF-2alpha phosphorylation was coincident with increased ***PEK*** autophosphorylation and eIF-2alpha kinase activity. Activation of ***PEK*** was abolished by ***deletion*** of ***PEK*** N-terminal sequences located in the ER lumen. To address the role of C. elegans ***PEK*** in translational control, we expressed this kinase in yeast and found that it inhibits growth by hyperphosphorylation of eIF-2alpha and inhibition of eIF-2B. Furthermore, we found that vaccinia virus K3L protein, an inhibitor of the eIF-2alpha kinase PKR involved in an anti-viral defence pathway, also reduced ***PEK*** activity. These results suggest that decreased translation initiation by ***PEK*** during ER stress may provide the cell with an opportunity to remedy the folding problem prior to introducing newly synthesized proteins into the secretory pathway.

L3 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1998:384564 CAPLUS
DN 129:160199
TI Skeletal muscle glycolytic capacity and phosphofructokinase regulation in horses with polysaccharide storage myopathy
AU Valberg, Stephanie J.; Townsend, Dewayne; Mickelson, James R.
CS Department of Clinical and Population Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, MN, 55108, USA
SO American Journal of Veterinary Research (1998), 59(6), 782-785
CODEN: AJVRAH; ISSN: 0002-9645
PB American Veterinary Medical Association
DT Journal
LA English
AB The aim was to det. whether polysaccharide storage myopathy (PSSM) in Quarter Horses is attributable to a defect in glycolysis or in the allosteric regulation of phosphofructokinase (***PEK***) enzyme. Muscle biopsy specimens were obtained from 6 Quarter Horses with PSSM and 8 Quarter Horse or Thoroughbred control horses. Maximal activity of glycogenolytic and glycolytic enzymes was detd. spectrophotometrically. Maximal activity of PFK was detd. for each horse at pH 8.0, and at pH 7.0 when variable concns. of the activators, fructose 6 phosphate, fructose 2,6 bisphosphate, and adenosine monophosphate or inhibitors ATP and citrate were added to the reaction mixt. Relative activity was calcd. as activity at pH 7/maximal PFK activity. ***Deficiencies*** in glycogenolytic or glycolytic enzyme activities were not evident in horses with PSSM. Differences between horses with PSSM and control horses in relative activity of PFK were not apparent for any of the activators or inhibitors used in the study. In a group of horses with PSSM, the authors were unable to detect a glycogenolytic or glycolytic enzyme ***deficiency*** or abnormality in the allosteric regulation of PFK. Although PSSM is clin. and histol. similar to glycogenolytic/glycolytic enzyme ***deficiencies*** in human beings and other animal species, abnormalities in this metabolic pathway are not present in horses with PSSM.
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 1994:181680 BIOSIS
DN PREV199497194680
TI Regulation of tyrosine hydroxylase gene expression in depolarized non-transformed bovine adrenal medullary cells: Second messenger systems and promoter mechanisms.
AU Stachowiak, Michal K. (1); Goc, Anna; Hong, Jau-Shyong; Poisner, Alan; Jiang, Hann-Kuang; Stachowiak, Ewa K.
CS (1) Lab. Mol. Neurobiol., Barrow Neurol. Inst., St. Joseph's Hosp. Med. Cent., 350 West Thomas Road, Phoenix, AZ 85013 USA
SO Molecular Brain Research, (1994) Vol. 22, No. 1-4, pp. 309-319. ISSN: 0169-328X.
DT Article
LA English
AB Activation of the tyrosine hydroxylase (TH) gene in the adrenal medulla during stress is mediated by trans-synaptic mechanisms and may involve cholinergic receptors. Stimulation of nicotinic receptors in adrenal medullary cells induces cell depolarization, influx of Ca-2+ ions and increases levels of cAMP. We have shown that both cAMP and membrane depolarization produce an increase in the expression of the TH gene in cultured bovine adrenal medullary cells (BAMC). Others have proposed that transcriptional activation of the TH gene by cAMP is mediated through the sequence homologous to a cAMP responsive element (CRE) located in the proximal region of the TH gene promoter. In the present study we have examined the mechanisms by which membrane depolarization increases the TH gene activity. Treatment of serum-free BAMC cultures with the depolarizing agent, veratridine, increased the extracellular concentration of catecholamines, Met-5-enkephalin, and the relative abundance of TH mRNA. Veratridine treatment also increased the levels of mRNAs for the catecholamine biosynthetic enzyme phenylethanolamine N-methyltransferase (PNMT), and proenkephalin A (***PEK***). Treatment for longer than 3 h was required to increase TH mRNA levels. By contrast, our previous studies indicated that cAMP stimulation for 2 h produces a maximal increase in TH mRNA levels in BAMC. The effects of veratridine and forskolin on TH mRNA levels were additive, further indicating that depolarization and cAMP activate TH gene expression via different pathways. Calmidazolium, an antagonist of calmodulin, had no effect on the veratridine-induced increase in TH mRNA levels. Similarly sphingosine treatment or

preincubation with PMA, which reduce protein kinase C (PKC) activity and attenuate the induction of TH mRNA by PMA or the hormone, angiotensin II, did not affect the induction by veratridine. To identify promoter mechanisms of TH gene activation in depolarized cells we transfected BAMC with a plasmid pTHgoodLuc and treated with veratridine for 24 h. pTHgoodLUC contains a luciferase reporter gene linked to a -428/+21 hp fragment of the bovine TH gene promoter (relative to the transcription start site). Veratridine increased the expression of luciferase from the TH promoter 2.5-fold. ***Deletion*** of the -194/-54 hp promoter region containing SP-1 and POU/Oct sites reduced veratridine stimulation by 40%. Additional ***deletion*** of the -269 to -190 hp promoter segment, including an AP-1 element, further reduced veratridine stimulation to a statistically non-significant level. In conclusion, activation of TH gene expression upon depolarization is not mediated by calmodulin and PKC. Promoter sequences involved in this activation are located upstream from the CRE. Depolarization may activate TH gene transcription by acting on more than one regulatory region.

L3 ANSWER 26 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 1985:411850 BIOSIS
DN BA80:81842
TI SLIT-LAMP MICROSCOPIC APPEARANCE OF CORNEAL WOUND HEALING AFTER RADIAL
KERATOTOMY.
AU WARING G O III; STEINBERG E B; WILSON L A
CS EMORY CLINIC, 1365 CLIFTON ROAD N.E., ATLANTA, GA. 30322.
SO AM J OPHTHALMOL, (1985) 100 (1), 218-224.
CODEN: AJOPAA. ISSN: 0002-9394.
FS BA; OLD
LA English
AB Radial keratotomy offers a unique opportunity to study corneal wound healing because the corneas are normal, the fine knife blades ***disrupt*** adjacent tissue minimally, no sutures are used, there is minimal inflammation, and few postoperative drugs are administered. Corneal wounds were studied with a slit-lamp microscope as they healed from 2 wk to three years after radial keratotomy in 84 eyes of 51 consecutive patients enrolled in the Prospective Evaluation of Radial Keratotomy (***PERK***) Study. One day after surgery, the incisions were surrounded by edema. At 2 wk, a dense, gray, diffusely marginated opacity occupied 0.1 mm on both sides of the incision. At 3 mo., the area adjacent to the incision was filled with discrete, fine, gray spicules that protruded at right angles from the incision. At 6 mo., the gray cloudiness had completely disappeared, and the individual spicules were more prominent. By 1 yr, the spicules were disappearing from the anterior portion of the incision and were concentrated primarily in the posterior part of the incisions. At 2 and 3 years, the incision scar was fainter and the spicules had disappeared from all but the deep posterior part of the wound. It is believed that these spicules correspond to the reorganization of the stroma along the edges of the corneal incision. The persistence of the spicules suggests that wound healing in radial keratotomy may not be complete > until 2 yr after surgery.

L3 ANSWER 27 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 85225282 EMBASE
DN 1985225282
TI Training, leadership and group composition: A review of the crucial variables.
AU Salvendy J.T.
CS St. Michael's Hospital, Toronto, Ont. M5B 1W8, Canada
SO Group Analysis, (1985) 18/2 (132-147).
CODEN: GRANEQ
CY United Kingdom
DT Journal
FS 032 Psychiatry
017 Public Health, Social Medicine and Epidemiology
LA English
AB A number of ***deficiencies*** and misconceptions associated with the group therapeutic education and practice have been reviewed. The following recommendations and comments are made: The rules for training in group psychotherapy should be firmed up, and as much as feasible made uniform in the various centres. The medical model, while under considerable attack for other reasons, can serve to demonstrate how insistence on certain standards allows for cross-regional and cross-country comparison and evaluation of the level of expertise attained. The demographic composition of a group is often unnecessarily restricted by an unsubstantiated 'rule' or through the neglectful handling of the non-common member. Any new 'band-wagon' phenomenon in group psychotherapy should be evaluated carefully, to ascertain that the primary beneficiaries are indeed the patients, and that one is not creating another ***perk*** or innovation for the sake of the therapist(s).

L3 ANSWER 28 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
AN 1977:178809 BIOSIS
DN BA64:1173
TI ESTABLISHMENT OF THE ORIGIN OF A PORCINE CELL LINE BY CHROMOSOME BANDING
TECHNIQUES AND SCANNING.
AU VAN WENT-DE VRIES G F; GISPEN R; DE FRANCE H F
SO J LAB CLIN MED, (1976) 88 (6), 965-970.
CODEN: JLCMAK. ISSN: 0022-2143.
FS BA; OLD
LA Unavailable
AB Use of cultured cells in diagnostic virology implies the necessity to establish the genetic origin of the cells. Chromosome analysis, performed on a cell line of pig embryo kidney cells (***PEK***), made the porcine origin of the cells plausible Definite proof was furnished by chromosome banding and scanning. A comparison was made between ***PEK***
-cells and normal pig chromosomes. Chromosomes No. 1 had an interstitial ***deletion*** , which provided a useful marker for identification purposes.

L3 ANSWER 29 OF 30 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1976:220245 BIOSIS
DN BA62:50245
TI CYTOLOGICAL STUDY OF A CONTINUOUS PIG EMBRYO KIDNEY CELL LINE WITH A
PERSISTENT TOXOPLASMA-GONDII INFECTION.
AU AKINSHINA G T; ZALKIND S YA
SO BYULL EKSP BIOL MED, (1975 (RECD 1976)) 80 (10), 122-125.
CODEN: BEBMAE. ISSN: 0365-9615.
FS BA; OLD
LA Unavailable
AB Invasion of the ***PEK*** [pig embryo kidney] cell culture by T. gondii caused no sharp ***disruption*** of the vital activity of the cells and did not result in their rapid degeneration. The observed changes in the morphology of host cells were apparently chiefly due to mechanical pressure of the vacuoles on the nucleus and the cytoplasm, although extreme disturbances of cell morphology possibly were associated with greater injury. Complete self-purification of the cells apparently did not occur. Despite the marked reduction in parasite numbers, later reinfection was possible.

L3 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1973:490996 CAPLUS
DN 79:90996
TI Identification and correction of copper ***deficiency*** of Rhododendron simsi George Lindley Taber cuttings
AU Dickey, R. D.
CS Ornamental Hortic. Dep., Inst. Food Agric. Sci., Gainesville, FL, USA
SO Proceedings of the Florida State Horticultural Society (1973), Volume Date 1972, 85, 398-400
CODEN: PFSHA7; ISSN: 0097-1219
DT Journal
LA English
AB A nutritional disorder of rooted cuttings of George Lindley Taber azalea, similar in appearance to previously identified Cu ***deficiency*** of Formosa and Fielder's White azaleas, was obsd. in a Florida nursery in June, 1971. Cu ***deficiency*** visual symptoms appeared on young leaves and twigs growing from terminal portions of the rooted cuttings; leaves and shoot growth were reduced in size. Some of the leaves developed tip burn, got slightly rumpled and twisted, esp. at the tips, some of the leaves dropped prematurely, and twigs died back. Chlorosis developed over the entire surface of the leaves. This disorder of rooted cuttings of George Lindley Taber azalea was corrected by Cu-contg. fertilizers. Cu was applied at rates equiv. to 10, 25, or 50 lb CuSO4/acre. All plants receiving CuSO4 or ***Perk*** grew normally, where 42% of the untreated plants died. There was no difference in size and quality of plants treated with either CuSO4 or ***Perk*** fertilizer.

=> s EIF2AK3
L4 16 EIF2AK3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 8 DUP REM L4 (8 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2002:398652 BIOSIS
DN PREV200200398652
TI Dimerization and release of molecular chaperone inhibition facilitate activation of eukaryotic initiation factor-2 kinase in response to endoplasmic reticulum stress.
AU Ma, Kun; Vattem, Krishna M.; Wek, Ronald C. (1)
CS (1) Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, 46202: rwek@iupui.edu USA
SO Journal of Biological Chemistry, (May 24, 2002) Vol. 277, No. 21, pp. 18728-18735. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Phosphorylation of eukaryotic initiation factor-2 (eIF2) by pancreatic eIF2 kinase (PEK), induces a program of translational expression in response to accumulation of malfolded protein in the endoplasmic reticulum (ER). This study addresses the mechanisms activating PEK, also designated

PERK or ***EIF2AK3*** . We describe the characterization of two regions in the ER luminal portion of the transmembrane PEK that carry out distinct functions in the regulation of this eIF2 kinase. The first region mediates oligomerization between PEK polypeptides, and deletion of this portion of PEK blocked induction of eIF2 kinase activity. The second characterized region of PEK facilitates interaction with ER chaperones. In the absence of stress, PEK associates with ER chaperones GRP78 (BiP) and GRP94, and this binding is released in response to ER stress. ER luminal sequences flanking the transmembrane domain are required for GRP78 interaction, and deletion of this portion of PEK led to its activation even in the absence of ER stress. These results suggest that this ER chaperone serves as a repressor of PEK activity, and release of ER chaperones from PEK when misfolded proteins accumulate in the ER induces gene expression required to enhance the protein folding capacity of the ER.

L5 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2002:416814 BIOSIS
DN PREV200200416814
TI Loss of kinase activity in a patient with Wolcott-Rallison syndrome caused by a novel mutation in the ***EIF2AK3*** gene.
AU Biason-Lauber, Anna (1); Lang-Muritano, Mariarosaria; Vaccaro, Tindara; Schoenle, Eugen J.
CS (1) Division of Endocrinology/Diabetology, University Children's Hospital, Steinwiesstrasse 75, 8032, Zurich: anna.lauber@kispi.unizh.ch Switzerland
SO Diabetes, (July, 2002) Vol. 51, No. 7, pp. 2301-2305. http://www.diabetes.org/Diabetes/. print.
ISSN: 0012-1797.
DT Article
LA English
AB Wolcott-Rallison syndrome (WRS) is an autosomal recessive disorder characterized by neonatal or early infancy type 1 diabetes, epiphyseal dysplasia, and growth retardation. Mutations in the ***EIF2AK3*** gene, encoding the eukaryotic initiation factor 2alpha-kinase 3 (***EIF2AK3***), have been found in WRS patients. Here we describe a girl who came to our attention at 2 months of age with severe hypertonic dehydration and diabetic ketoacidosis. A diagnosis of type 1 diabetes was made and insulin treatment initiated. Growth retardation and microcephaly were also present. Anti-islet cell autoantibodies were negative, and mitochondrial diabetes was excluded. Imaging revealed a hypoplastic pancreas and typical signs of spondylo-epiphyseal dysplasia. The diagnosis of WRS was therefore made at age 5 years. Sequencing analysis of her ***EIF2AK3*** gene revealed the presence of a homozygous T to C exchange in exon 13 leading to the missense serine 877 proline mutation. The mutated kinase, although it partly retains the ability of autophosphorylation, is unable to phosphorylate its natural substrate, eukaryotic initiation factor 2alpha (eIF2alpha). This is the first case in which the pathophysiological role of ***EIF2AK3*** deficiency in WRS is confirmed at the molecular level. Our data demonstrate that ***EIF2AK3*** kinase activity is essential for pancreas islet function and bone development in humans, and we suggest ***EIF2AK3*** as a possible target for therapeutic intervention in diabetes.

L5 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:371684 BIOSIS
DN PREV200100371684
TI No evidence for diabetes-associated mutations of PEK/ ***EIF2AK3*** gene in French patients with early-onset Type II diabetes.
AU Vaxillaire, M. (1); Benmezroua, Y.; Durand, E.; Vasseur, F.; Froguel, P.
CS (1) CNRS EP 10, Institut de Biologie de Lille, Institut Pasteur de Lille, 1 Rue du Pr. Calmette, 59019, Lille Cedex France
SO Diabetologia, (June, 2001) Vol. 44, No. 6, pp. 786. print.
ISSN: 0012-186X.
DT Letter
LA English
SL English

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 2001:868690 CAPLUS
DN 136:18871
TI A mutation in the ***EIF2AK3*** gene for eukaryotic translation initiation factor 2.alpha. kinase 3 in patients with neonatal insulin-dependent diabetes and multiple epiphyseal dysplasia (Wolcott-Rallison syndrome)
IN Julier, Cecile; Delepine, Marc; Nicolino, Marc
PA Institut National De La Sante Et De La Recherche Medicale (INSERM), Fr.; Centre National De Genotypage
SO PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001090371	A1	20011129	WO 2001-IB1153	20010523
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1283889	A1	20030219	EP 2001-943730	20010523
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI EP 2000-401436	A	20000523		
EP 2000-402707	A	20001002		
WO 2001-IB1153	W	20010523		

AB The present invention is directed to isolated variant nucleic sequence of genomic sequence encoding the translation initiation factor 2 alpha kinase 3 (***EIF2AK3***) capable of inducing the Wolcott-Rallison syndrome (WRS) or affecting the risk of developing diabetes and/or other pathol. related to WRS, and to the polypeptide encoded by these sequences. The invention also relates to vectors or transformed cells contg. these sequences. The present invention further concerns method and kit for detg. in a subject the risk of developing diabetes and/or other pathol. related to WRS and method for selecting compd. which can be used as medicament for the prevention and/or treatment of these pathologies.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
AN 2001321850 EMBASE
TI No evidence for diabetes-associated mutations of PEK/ ***EIF2AK3*** gene in French patients with early-onset type II diabetes [4].
AU Vaxillaire M.
CS Dr. M. Vaxillaire, CNRS EP 10, Institut de Biologie de Lille, Institut Pasteur de Lille, 1 rue du Pr. Calmette, 59019 Lille Cedex, France
SO Diabetologia, (2001) 44/6 (786).
Refs: 7
ISSN: 0012-186X CODEN: DBTGAJ
CY Germany
DT Journal; Letter
FS 004 Microbiology
006 Internal Medicine
022 Human Genetics
LA English

L5 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:70135 BIOSIS
DN PREV200200070135
TI Novel mutation in the ***EIF2AK3*** gene in a case of Wolcott-Rallison syndrome.
AU Biason-Lauber, A. (1); Lang-Muritano, M. (1); Schoenle, E. J. (1)
CS (1) Ped Endocrinology/Diabetology, Univ Children's Hosp, Zurich Switzerland
SO American Journal of Human Genetics, (October, 2001) Vol. 69, No. 4 Supplement, pp. 615. http://www.journals.uchicago.edu/AJHG/home.html. print.
Meeting Info.: 51st Annual Meeting of the American Society of Human Genetics San Diego, California, USA October 12-16, 2001
ISSN: 0002-9297.
DT Conference
LA English

L5 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2000:452481 BIOSIS
DN PREV200000452481
TI ***EIF2AK3*** , encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome.
AU Delepine, Marc; Nicolino, Marc; Barrett, Timothy; Golamaully, Mahamadee; Lathrop, G. Mark; Julier, Cecile (1)
CS (1) Wellcome Trust Centre for Human Genetics, Oxford UK
SO Nature Genetics, (August, 2000) Vol. 25, No. 4, pp. 406-409. print.
ISSN: 1061-4036.
DT Article
LA English
SL English
AB Wolcott-Rallison syndrome (WRS) is a rare, autosomal recessive disorder characterized by permanent neonatal or early infancy insulin-dependent diabetes. Epiphyseal dysplasia, osteoporosis and growth retardation occur at a later age. Other frequent multisystemic manifestations include hepatic and renal dysfunction, mental retardation and cardiovascular abnormalities. On the basis of two consanguineous families, we mapped WRS to a region of less than 3 cM on chromosome 2p12, with maximal evidence of linkage and homozygosity at 4 microsatellite markers within an interval of approximately 1 cM. The gene encoding the eukaryotic translation initiation factor 2-alpha kinase 3 (***EIF2AK3***) resides in this interval; thus we explored it as a candidate. We identified distinct mutations of ***EIF2AK3*** that segregated with the disorder in each of the families. The first mutation produces a truncated protein in which the entire catalytic domain is missing. The other changes an amino acid, located in the catalytic domain of the protein, that is highly conserved among kinases from the same subfamily. Our results provide evidence for the role of ***EIF2AK3*** in WRS. The identification of this gene may provide insight into the understanding of the more common forms of diabetes and other pathologic manifestations of WRS.

L5 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2000:49737 BIOSIS
DN PREV200000049737
TI Assignment of pancreatic eIF-2alpha kinase (***EIF2AK3***) to human chromosome band 2p 12 by radiation hybrid mapping and in situ

hybridization.
AU Hayes, S. E.; Conner, L. J.; Stramm, L. E.; Shi, Y. (1)
CS (1) Endocrine Division, DC0545, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN USA
SO Cytogenetics and Cell Genetics, (1999) Vol. 86, No. 3-4, pp. 327-328. ISSN: 0301-0171.
DT Article
LA English

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		105.53	105.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	ENTRY	SINCE FILE SESSION	TOTAL
CA SUBSCRIBER PRICE		-8.46	-8.46

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WEST Search History

DATE: Thursday, April 10, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,DWPI; PLUR=YES; OP=ADJ			
L3	type I transmembrane ER resident serine threonine protein kinase	1	L3
L2	L1 same (knockout or knock-out or transgen$ or disrupt$ or deficien$ or deleti$)	6	L2
L1	PERK	740	L1

END OF SEARCH HISTORY